

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number  
WO 02/055082 A1(51) International Patent Classification<sup>7</sup>: A61K 31/505,  
C07D 487/04, A61P 25/28 // (C07D 487/04, 239:00,  
231:00)(74) Agents: COCKERTON, Bruce, Roger et al.; Carpmals  
& Ransford, 43 Bloomsbury Square, London WC1A 2RA  
(GB).

(21) International Application Number: PCT/GB02/00075

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,  
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,  
VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 10 January 2002 (10.01.2002)

(25) Filing Language: English

(26) Publication Language: English

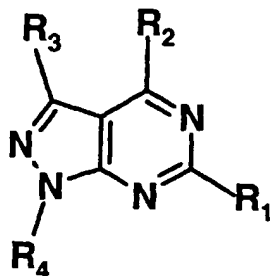
(30) Priority Data:  
0100621.2 10 January 2001 (10.01.2001) GB(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
NE, SN, TD, TG).(71) Applicant (*for all designated States except US*): VER-  
NALIS RESEARCH LIMITED [GB/GB]; Oakdene  
Court, 613 Reading Road, Winnersh, Wokingham RG41  
5UA (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): GILLESPIE,  
Roger, John [GB/GB]; Oakdene Court, 613 Read-  
ing Road, Winnersh, Wokingham RG41 5UA (GB).  
LERPINIERE, Joanne [GB/GB]; Oakdene Court, 613  
Reading Road, Winnersh, Wokingham RG41 5UA (GB).  
GAUR, Suneel [GB/GB]; Oakdene Court, 613 Reading  
Road, Winnersh, Wokingham RG41 5UA (GB).**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: PYRAZOLO[3,4-D]PYRIMIDINE DERIVATIVES AND THEIR USE AS PURINERGIC RECEPTOR ANTAG-  
ONISTS

(I)

(57) **Abstract:** Use of a compound of formula (I): wherein R<sub>1</sub> is selected from alkyl, alkoxy, aryloxy, alkylthio, arylthio, aryl, halogen, CN, NR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>COR<sub>6</sub>, NR<sub>5</sub>CONR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>CO<sub>2</sub>R<sub>8</sub> and NR<sub>5</sub>SO<sub>2</sub>R<sub>8</sub>; R<sub>2</sub> is selected from heteroaryl attached via an unsaturated carbon; R<sub>3</sub> is selected from H, alkyl, halogen, OR<sub>5</sub>, SR<sub>5</sub> and NR<sub>6</sub>R<sub>7</sub>; R<sub>4</sub> is selected from H, acyclic alkyl, CONR<sub>6</sub>R<sub>7</sub>, CONR<sub>5</sub>NR<sub>6</sub>R<sub>7</sub>, COR<sub>6</sub>, CO<sub>2</sub>R<sub>8</sub> and SO<sub>2</sub>R<sub>8</sub>; R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are independently selected from H, alkyl and aryl, or where R<sub>6</sub> and R<sub>7</sub> are in an NR<sub>6</sub>R<sub>7</sub> group, R<sub>6</sub> and R<sub>7</sub> may be linked to form a heterocyclic group, or where R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are in a (CONR<sub>5</sub>NR<sub>6</sub>R<sub>7</sub>) group, R<sub>5</sub> and R<sub>6</sub> may be linked to form a heterocyclic group; and R<sub>8</sub> is selected from alkyl and aryl, or a pharmaceutically acceptable salt thereof or prodrug thereof, in the treatment or prevention of a disorder in which the blocking of purine receptors, particularly adenosine receptors and more particularly A<sub>2A</sub> receptors, may be beneficial, particularly wherein said disorder is a movement disorder such as Parkinson's disease or said disorder is

depression, cognitive or memory impairment, acute or chronic pain, ADHD or narcolepsy, or for neuroprotection in a subject; compounds of formula (I) for use in therapy; and novel compounds of formula (I) *per se*.

WO 02/055082 A1

**PYRAZOLO[3,4-d]PYRIMIDINE DERIVATIVES AND THEIR USE AS  
PURINERGIC RECEPTOR ANTAGONISTS**

5 The present invention relates to pyrazolo[3,4-d]pyrimidine derivatives and their use in therapy. In particular, the present invention relates to the treatment of disorders in which the reduction of purinergic neurotransmission could be beneficial. The invention relates in particular to the blockade of adenosine receptors and particularly adenosine A<sub>2A</sub> receptors, and to the treatment of movement disorders such as Parkinson's disease.

10

Movement disorders constitute a serious health problem, especially amongst the elderly sector of the population. These movement disorders are often the result of brain lesions. Disorders involving the basal ganglia which result in movement disorders include Parkinson's disease, Huntington's chorea and Wilson's disease. Furthermore, dyskinesias

15 often arise as sequelae of cerebral ischaemia and other neurological disorders.

There are four classic symptoms of Parkinson's disease: tremor, rigidity, akinesia and postural changes. The disease is also commonly associated with depression, dementia and overall cognitive decline. Parkinson's disease has a prevalence of 1 per 1,000 of the total

20 population. The incidence increases to 1 per 100 for those aged over 60 years. Degeneration of dopaminergic neurones in the substantia nigra and the subsequent reductions in interstitial concentrations of dopamine in the striatum are critical to the development of Parkinson's disease. Some 80% of cells from the substantia nigra need to be destroyed before the clinical symptoms of Parkinson's disease are manifested.

25

Current strategies for the treatment of Parkinson's disease are based on transmitter replacement therapy (L-dihydroxyphenylacetic acid (L-DOPA)), inhibition of monoamine oxidase (e.g. Deprenyl<sup>®</sup>), dopamine receptor agonists (e.g. bromocriptine and apomorphine) and anticholinergics (e.g. benztrrophine, orphenadrine). Transmitter

30 replacement therapy in particular does not provide consistent clinical benefit, especially after prolonged treatment when "on-off" symptoms develop, and this treatment has also been associated with involuntary movements of athetosis and chorea, nausea and vomiting. Additionally current therapies do not treat the underlying neurodegenerative disorder

resulting in a continuing cognitive decline in patients. Despite new drug approvals, there is still a medical need in terms of improved therapies for movement disorders, especially Parkinson's disease. In particular, effective treatments requiring less frequent dosing, effective treatments which are associated with less severe side-effects, and effective  
5 treatments which control or reverse the underlying neurodegenerative disorder, are required.

Blockade of A<sub>2</sub> adenosine receptors has recently been implicated in the treatment of movement disorders such as Parkinson's disease (Richardson, P.J. *et al.*, *Trends Pharmacol. Sci.* 1997, 18, 338-344) and in the treatment of cerebral ischaemia (Gao, Y. and Phillis, J.W., *Life Sci.* 1994, 55, 61-65). The potential utility of adenosine A<sub>2A</sub> receptor antagonists in the treatment of movement disorders such as Parkinson's Disease has recently been reviewed (Mally, J. and Stone, T.W., *CNS Drugs*, 1998, 10, 311-320).

15 Adenosine is a naturally occurring purine nucleoside which has a wide variety of well-documented regulatory functions and physiological effects. The central nervous system (CNS) effects of this endogenous nucleoside have attracted particular attention in drug discovery, owing to the therapeutic potential of purinergic agents in CNS disorders (Jacobson, K.A. *et al.*, *J. Med. Chem.* 1992, 35, 407-422). This therapeutic potential has  
20 resulted in considerable recent research endeavour within the field of adenosine receptor agonists and antagonists (Bhagwhat, S.S.; Williams, M. *Exp. Opin. Ther. Patents* 1995, 5, 547-558).

Adenosine receptors represent a subclass (P<sub>1</sub>) of the group of purine nucleotide and  
25 nucleoside receptors known as purinoreceptors. The main pharmacologically distinct adenosine receptor subtypes are known as A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> (of high and low affinity) and A<sub>3</sub> (Fredholm, B.B., *et al.*, *Pharmacol. Rev.* 1994, 46, 143-156). The adenosine receptors are present in the CNS (Fredholm, B.B., *News Physiol. Sci.*, 1995, 10, 122-128).

30 The design of P<sub>1</sub> receptor-mediated agents has been reviewed (Jacobson, K.A., Suzuki, F., *Drug Dev. Res.*, 1997, 39, 289-300; Baraldi, P.G. *et al.*, *Curr. Med. Chem.* 1995, 2, 707-722), and such compounds are claimed to be useful in the treatment of cerebral ischemia or neurodegenerative disorders, such as Parkinson's disease (Williams, M. and Burnstock, G.

*Purinergic Approaches Exp. Ther.* (1997), 3-26. Editor: Jacobson, Kenneth A.; Jarvis, Michael F. Publisher: Wiley-Liss, New York, N.Y.)

It has been speculated that xanthine derivatives such as caffeine may offer a form of  
5 treatment for attention-deficit hyperactivity disorder (ADHD). A number of studies have  
demonstrated a beneficial effect of caffeine on controlling the symptoms of ADHD  
(Garfinkel, B.D. *et al.*, *Psychiatry*, 1981, **26**, 395-401). Antagonism of adenosine receptors  
is thought to account for the majority of the behavioural effects of caffeine in humans and  
thus blockade of adenosine A<sub>2A</sub> receptors may account for the observed effects of caffeine  
10 in ADHD patients. Therefore a selective A<sub>2A</sub> receptor antagonist may provide an effective  
treatment for ADHD but without the unwanted side-effects associated with current therapy.

Adenosine receptors have been recognised to play an important role in regulation of sleep  
patterns, and indeed adenosine antagonists such as caffeine exert potent stimulant effects  
15 and can be used to prolong wakefulness (Porkka-Heiskanen, T. *et al.*, *Science*, 1997, **276**,  
1265-1268). Recent evidence suggests that a substantial part of the actions of adenosine in  
regulating sleep is mediated through the adenosine A<sub>2A</sub> receptor (Satoh, S., *et al.*, *Proc.*  
*Natl. Acad. Sci.*, USA, 1996). Thus, a selective A<sub>2A</sub> receptor antagonist may be of benefit in  
counteracting excessive sleepiness in sleep disorders such as hypersomnia or narcolepsy.

20

It has recently been observed that patients with major depression demonstrate a blunted  
response to adenosine agonist-induced stimulation in platelets, suggesting that a  
dysregulation of A<sub>2A</sub> receptor function may occur during depression (Berk, M. *et al.*, 2001,  
*Eur. Neuropsychopharmacol.* 11, 183-186). Experimental evidence in animal models has  
25 shown that blockade of A<sub>2A</sub> receptor function confers antidepressant activity (El Yacoubi,  
M *et al.* *Br. J. Pharmacol.* 2001, 134, 68-77). Thus, A<sub>2A</sub> receptor antagonists may offer a  
novel therapy for the treatment of major depression and other affective disorders in  
patients.

30 The pharmacology of adenosine A<sub>2A</sub> receptors has been reviewed (Ongini, E.; Fredholm,  
B.B. *Trends Pharmacol. Sci.* 1996, 17(10), 364-372). One potential underlying mechanism  
in the aforementioned treatment of movement disorders by the blockade of A<sub>2</sub> adenosine  
receptors is the evidence of a functional link between adenosine A<sub>2A</sub> receptors to dopamine

D<sub>2</sub> receptors in the CNS. Some of the early studies (e.g. Ferre, S. *et al.*, Stimulation of high-affinity adenosine A<sub>2</sub> receptors decreases the affinity of dopamine D<sub>2</sub> receptors in rat striatal membranes. *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88, 7238-41) have been summarised in two more recent articles (Fuxe, K. *et al.*, *Adenosine Adenine Nucleotides* 5 *Mol. Biol. Integr. Physiol.*, [Proc. Int. Symp.], 5th (1995), 499-507. Editors: Belardinelli, Luiz; Pelleg, Amir. Publisher: Kluwer, Boston, Mass.; Ferre, S. *et al.*, *Trends Neurosci.* 1997, 20, 482-487).

As a result of these investigations into the functional role of adenosine A<sub>2A</sub> receptors in the 10 CNS, especially *in vivo* studies linking A<sub>2</sub> receptors with catalepsy (Ferre *et al.*, *Neurosci. Lett.* 1991, 130, 162-4; Mandhane, S.N. *et al.*, *Eur. J. Pharmacol.* 1997, 328, 135-141) investigations have been made into agents which selectively bind to adenosine A<sub>2A</sub> receptors as potentially effective treatments for Parkinson's disease.

15 While many of the potential drugs for treatment of Parkinson's disease have shown benefit in the treatment of movement disorders, an advantage of adenosine A<sub>2A</sub> antagonist therapy is that the underlying neurodegenerative disorder may also be treated. The neuroprotective effect of adenosine A<sub>2A</sub> antagonists has been reviewed (Ongini, E.; Adami, M.; Ferri, C.; Bertorelli, R., *Ann. N. Y. Acad. Sci.* 1997, 825(Neuroprotective Agents), 30-48). In 20 particular, compelling recent evidence suggests that blockade of A<sub>2A</sub> receptor function confers neuroprotection against MPTP-induced neurotoxicity in mice (Chen, J-F., *J. Neurosci.* 2001, 21, RC143). In addition, several recent studies have shown that consumption of dietary caffeine, a known adenosine A<sub>2A</sub> receptor antagonist, is associated with a reduced risk of Parkinson's disease in man (Ascherio, A. *et al.*, *Ann Neurol.*, 2001, 25 50, 56-63; Ross G W, *et al.*, *JAMA*, 2000, 283, 2674-9). Thus, A<sub>2A</sub> receptor antagonists may offer a novel treatment for conferring neuroprotection in neurodegenerative diseases such as Parkinson's disease.

Xanthine derivatives have been disclosed as adenosine A<sub>2</sub> receptor antagonists as useful for 30 treating various diseases caused by hyperfunctioning of adenosine A<sub>2</sub> receptors, such as Parkinson's disease (see, for example, EP-A-565377).

One prominent xanthine-derived adenosine A<sub>2A</sub> selective antagonist is CSC [8-(3-chlorostyryl)caffeine] (Jacobson *et al.*, *FEBS Lett.*, 1993, 323, 141-144).

Theophylline (1,3-dimethylxanthine), a bronchodilator drug which is a mixed antagonist at  
5 adenosine A<sub>1</sub> and A<sub>2A</sub> receptors, has been studied clinically. To determine whether a  
formulation of this adenosine receptor antagonist would be of value in Parkinson's disease  
an open trial was conducted on 15 Parkinsonian patients, treated for up to 12 weeks with a  
slow release oral theophylline preparation (150 mg/day), yielding serum theophylline levels  
of 4.44 mg/L after one week. The patients exhibited significant improvements in mean  
10 objective disability scores and 11 reported moderate or marked subjective improvement  
(Mally, J., Stone, T.W., *J. Pharm. Pharmacol.* 1994, 46, 515-517).

KF 17837 [(E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine] is a selective  
adenosine A<sub>2A</sub> receptor antagonist which on oral administration significantly ameliorated  
15 the cataleptic responses induced by intracerebroventricular administration of an adenosine  
A<sub>2A</sub> receptor agonist, CGS 21680. KF 17837 also reduced the catalepsy induced by  
haloperidol and reserpine. Moreover, KF 17837 potentiated the anticataleptic effects of a  
subthreshold dose of L-DOPA plus benserazide, suggesting that KF 17837 is a centrally  
active adenosine A<sub>2A</sub> receptor antagonist and that the dopaminergic function of the  
20 nigrostriatal pathway is potentiated by adenosine A<sub>2A</sub> receptor antagonists (Kanda, T. *et al.*,  
*Eur. J. Pharmacol.* 1994, 256, 263-268). The structure activity relationship (SAR) of KF  
17837 has been published (Shimada, J. *et al.*, *Bioorg. Med. Chem. Lett.* 1997, 7, 2349-  
2352). Recent data has also been provided on the A<sub>2A</sub> receptor antagonist KW-6002  
(Kuwana, Y *et al.*, *Soc. Neurosci. Abstr.* 1997, 23, 119.14; and Kanda, T. *et al.*, *Ann.*  
25 *Neurol.* 1998, 43(4), 507-513).

New non-xanthine structures sharing these pharmacological properties include SCH 58261  
and its derivatives (Baraldi, P.G. *et al.*, Pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine  
Derivatives: Potent and Selective A<sub>2A</sub> Adenosine Antagonists. *J. Med. Chem.* 1996, 39,  
30 1164-71). SCH 58261 (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-e]-1,2,4-  
triazolo[1,5-c] pyrimidine) is reported as effective in the treatment of movement disorders  
(Ongini, E. *Drug Dev. Res.* 1997, 42(2), 63-70) and has been followed up by a later series  
of compounds (Baraldi, P.G. *et al.*, *J. Med. Chem.* 1998, 41(12), 2126-2133).

The foregoing discussion indicates that a potentially effective treatment for movement disorders in humans would comprise agents which act as antagonists at adenosine A<sub>2A</sub> receptors.

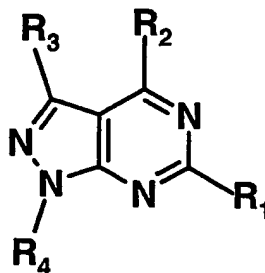
5

It has now been found that pyrazolo[3,4-d]pyrimidine derivatives, which are structurally unrelated to known adenosine receptor antagonists, exhibit unexpected antagonist binding affinity at adenosine (P<sub>1</sub>) receptors, and in particular at the adenosine A<sub>2A</sub> receptor. Such compounds may therefore be useful for the treatment of disorders in which the blocking of  
10 purine receptors, particularly adenosine receptors and more particularly adenosine A<sub>2A</sub> receptors, may be beneficial. In particular, such compounds may be suitable for the treatment of movement disorders, such as disorders of the basal ganglia which result in dyskinesias. Disorders of particular interest in the present invention include Parkinson's disease, Alzheimer's disease, spasticity, Huntington's chorea and Wilson's disease.

15

Such compounds may also be particularly suitable for the treatment of depression, cognitive or memory impairment including Alzheimer's disease, acute or chronic pain, ADHD, narcolepsy or for neuroprotection.

20 According to the present invention there is provided the use of a compound of formula (I):



(I)

25 wherein

R<sub>1</sub> is selected from alkyl, alkoxy, aryloxy, alkylthio, arylthio, aryl, halogen, CN, NR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>COR<sub>6</sub>, NR<sub>5</sub>CONR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>CO<sub>2</sub>R<sub>8</sub> and NR<sub>5</sub>SO<sub>2</sub>R<sub>8</sub>;

R<sub>2</sub> is selected from heteroaryl attached via an unsaturated carbon of said heteroaryl;

R<sub>3</sub> is selected from H, alkyl, halogen, OR<sub>5</sub>, SR<sub>5</sub> and NR<sub>6</sub>R<sub>7</sub>;

R<sub>4</sub> is selected from H, acyclic alkyl, CONR<sub>6</sub>R<sub>7</sub>, CONR<sub>5</sub>NR<sub>6</sub>R<sub>7</sub>, COR<sub>6</sub>, CO<sub>2</sub>R<sub>8</sub> and SO<sub>2</sub>R<sub>8</sub>;

R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are independently selected from H, alkyl and aryl or where R<sub>6</sub> and R<sub>7</sub> are in an NR<sub>6</sub>R<sub>7</sub> group R<sub>6</sub> and R<sub>7</sub> may be linked to form a heterocyclic group, or where R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub>

5 are in a (CONR<sub>5</sub>NR<sub>6</sub>R<sub>7</sub>) group, R<sub>5</sub> and R<sub>6</sub> may be linked to form a heterocyclic group; and  
R<sub>8</sub> is selected from alkyl and aryl,

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a disorder in which the blocking of purine receptors, particularly adenosine receptors and more particularly A<sub>2A</sub> receptors, may be  
10 beneficial.

As used herein the term "alkyl", unless otherwise stated, means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical which may be substituted or unsubstituted. Where cyclic, the alkyl group is preferably C<sub>3</sub> to C<sub>12</sub>,  
15 more preferably C<sub>5</sub> to C<sub>10</sub>, more preferably C<sub>5</sub>, C<sub>6</sub> or C<sub>7</sub>. Where acyclic, the alkyl group is preferably C<sub>1</sub> to C<sub>10</sub>, more preferably C<sub>1</sub> to C<sub>6</sub>, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and isopentyl), more preferably methyl. It will be appreciated therefore that the term "alkyl" as used herein, unless otherwise stated, includes alkyl (branched or unbranched), alkenyl (branched or  
20 unbranched), alkynyl (branched or unbranched), cycloalkyl, cycloalkenyl and cycloalkynyl.

As used herein, the term "lower alkyl" means methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl).

25 As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl (preferably phenyl), or a heteroaromatic group containing one or more heteroatom(s) preferably selected from N, O and S, such as pyridyl, pyrrolyl, quinoliny, furanyl, thienyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, triazolyl, imidazolyl, pyrimidinyl, indolyl, pyrazinyl and indazolyl.

30

As used herein, the term "heteroaryl" means an aromatic group containing one or more heteroatom(s) preferably selected from N, O and S, such as pyridyl, pyrrolyl, quinoliny,



furanyl, thienyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, triazolyl, imidazolyl, pyrimidinyl, indolyl, pyrazinyl and indazolyl..

As used herein, the term "non-aromatic heterocyclyl" means a non-aromatic cyclic group  
5 containing one or more heteroatom(s) preferably selected from N, O and S, such as a cyclic amino group (including aziridinyl, azetidiny, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl) or a cyclic ether (including tetrahydrofuranyl).

As used herein, the term "alkoxy" means alkyl-O-. As used herein, the term "aryloxy" means  
10 aryl-O-.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical.

As used herein, the term "ortho,ortho-disubstituted aryl groups" refers to heteroaryl groups  
15 which are substituted in both ortho positions of the heteroaryl group relative to the point of attachment of the heteroaryl group to the pyrimidine ring.

As used herein, the term "prodrug" means any pharmaceutically acceptable prodrug of a  
20 compound of the present invention.

Where any of R<sub>1</sub> to R<sub>14</sub> is selected from alkyl, alkoxy and thioalkyl, in accordance with formula (I) as defined above, then that alkyl group, or the alkyl group of the alkoxy or thioalkyl group, may be substituted or unsubstituted. Where any of R<sub>1</sub> to R<sub>14</sub> are selected from aryl, aryloxy and thioaryl, in accordance with formula (I) as defined above, then said  
25 aryl group, or the aryl group of the aryloxy or thioaryl group, may be substituted or unsubstituted. Where R<sub>6</sub> and R<sub>7</sub>, or R<sub>5</sub> and R<sub>6</sub>, are linked to form a heterocyclic group, the heterocyclic group may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include: carbon-containing groups such as

30 alkyl,  
aryl, (e.g. substituted and unsubstituted phenyl (including (alkyl)phenyl, (alkoxy)phenyl, (alkyl- and aryl-sulfonylamino)phenyl and halophenyl),

- arylalkyl; (e.g. substituted and unsubstituted benzyl);
- halogen atoms and halogen containing groups such as
- haloalkyl (e.g. trifluoromethyl),
- haloaryl (e.g. chlorophenyl);
- 5 oxygen containing groups such as
- alcohols (e.g. hydroxy, hydroxyalkyl, hydroxyaryl, (aryl)(hydroxy)alkyl),
- ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl, alkoxyaryl, aryloxyaryl),
- 10 aldehydes (e.g. carboxaldehyde),
- ketones (e.g. alkylcarbonyl, arylcarbonyl, alkylcarbonylalkyl, alkylcarbonylaryl, arylcarbonylalkyl, arylcarbonylaryl, arylalkylcarbonyl, arylalkylcarbonylalkyl, arylalkylcarbonylaryl)
- 15 acids (e.g. carboxy, carboxyalkyl, carboxyaryl),
- acid derivatives such as esters
- (e.g. alkoxycarbonyl, aryloxcarbonyl, alkoxycarbonylalkyl, aryloxcarbonylalkyl, alkoxycarbonylaryl, aryloxcarbonylaryl, alkylcarbonyloxy, alkylcarbonyloxyalkyl),
- 20 amides
- (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, cyclicaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl or arylalkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino or arylalkylcarbonylamino),
- 25 carbamates
- (eg. alkoxycarbonylamino, aryloxcarbonylamino, arylalkyloxcarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylaminocarbonyloxy or arylalkylaminocarbonyloxy)
- 30 and ureas

(eg. mono- or di-alkylaminocarbonylamino, arylaminocarbonylamino or arylalkylaminocarbonylamino);

nitrogen containing groups such as

- 5 amines (e.g. amino, mono- or dialkylamino, cyclicamino, arylamino, aminoalkyl, mono- or dialkylaminoalkyl),
- azides,
- nitrides (e.g. cyano, cyanoalkyl),
- nitro,
- 10 sulfonamides (e.g. aminosulfonyl, mono- or di-alkylaminosulfonyl, mono- or di-arylamino sulfonyl, alkyl- or aryl-sulfonylamino, alkyl- or aryl-sulfonyl(alkyl)amino, alkyl- or aryl-sulfonyl(aryl)amino);

sulfur containing groups such as

- 15 thiols, thioethers, sulfoxides, and sulfones
- (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl)
- 20 and heterocyclic groups containing one or more, preferably one, heteroatom,
- (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidiny, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoliny, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl,
- 25
- 30

quinoxaliny, chromenyl, chromanyl, isochromanyl,  
phthalazinyl and carbolinyl).

Where any of R<sub>1</sub> to R<sub>14</sub> is selected from aryl or from an aryl-containing group such as aryloxy  
5 or arylthio, preferred substituent group(s) are selected from halogen, alkyl (substituted or  
unsubstituted; and where substituted particularly from alkoxyalkyl, hydroxyalkyl, aminoalkyl  
and haloalkyl), hydroxy, alkoxy, CN, NO<sub>2</sub>, amines (including amino, mono- and di-  
alkylamino), alkoxycarbonyl, aminocarbonyl, carboxamido, sulfonamido,  
alkoxycarbonylamino and aryl, and particularly from unsubstituted alkyl, substituted alkyl  
10 (including alkoxyalkyl and aminoalkyl), halogen and amines.

In one embodiment, where any of R<sub>1</sub> to R<sub>14</sub> is directly substituted by an alkyl substituent  
group, or by an alkyl-containing substituent group (such as alkoxy or alkylcarbonylamino for  
example), then the alkyl moiety of the substituent group directly attached to any of R<sub>1</sub> to R<sub>14</sub>  
15 may be further substituted by the substituent groups hereinbefore described and particularly by  
halogen, hydroxy, alkoxy, CN, amines (including amino, mono- and di-alkyl amino) and aryl.

In a further embodiment, where any of R<sub>1</sub> to R<sub>14</sub> is directly substituted by an aryl substituent  
group, or by an aryl-containing substituent group (such as aryloxy or arylaminocarbonylamino  
20 for example), then the aryl moiety of the substituent group directly attached to any of R<sub>1</sub> to R<sub>14</sub>  
may be further substituted by the substituent groups hereinbefore described and particularly by  
halogen, alkyl (substituted or unsubstituted; and where substituted particularly from  
alkoxyalkyl, hydroxyalkyl, aminoalkyl and haloalkyl), hydroxy, alkoxy, CN, NO<sub>2</sub>, amines  
(including amino, mono- and di-alkylamino), alkoxycarbonyl, aminocarbonyl, carboxamido,  
25 sulfonamido, alkoxycarbonylamino and aryl. In a further embodiment, said aryl moiety is  
substituted by halogen, alkyl (including CF<sub>3</sub>), hydroxy, alkoxy, CN, amines (including amino,  
mono- and di-alkyl amino) and NO<sub>2</sub>. In a further embodiment, said aryl moiety is substituted  
by unsubstituted alkyl, substituted alkyl (particularly alkoxyalkyl and aminoalkyl), halogen and  
amines.

The terms "directly substituted" and "directly attached", as used herein, mean that the substituent group is bound directly to any of  $R_1$  to  $R_{14}$  without any intervening divalent atoms or groups.

- 5 In the compounds of formula (I),  $R_1$  is selected from alkyl (including branched and unbranched alkyl, substituted and unsubstituted alkyl, and cyclic and acyclic alkyl), alkoxy, aryloxy, alkylthio, arylthio, aryl (including heteroaryl), halogen, CN,  $NR_6R_7$  (including  $NH_2$ , mono-alkylamino and di-alkylamino),  $NR_5COR_6$ ,  $NR_5CONR_6R_7$ ,  $NR_5CO_2R_8$  and  $NR_5SO_2R_8$ .

10

Where  $R_1$  is selected from alkyl, alkoxy and alkylthio, then said alkyl group or the alkyl group of the alkoxy or alkylthio is preferably selected from  $C_{1-6}$  alkyl (including branched and unbranched alkyl, substituted and unsubstituted alkyl, and cyclic and acyclic alkyl), preferably saturated  $C_{1-6}$  alkyl, and more preferably lower alkyl. In one embodiment,  $R_1$  is selected from  
15 substituted alkyl, particularly haloalkyl (including  $CF_3$ ) and arylalkyl (including heteroarylalkyl), and particularly haloalkyl (including  $CF_3$ ).

Where  $R_1$  is selected from  $NR_5CONR_6R_7$ ,  $NR_5COR_6$ ,  $NR_5CO_2R_8$  and  $NR_5SO_2R_8$ , preferably  $R_5$  is H or alkyl, and preferably H.

20

It is preferred that  $R_1$  is selected from alkyl, alkoxy, thioalkyl,  $NR_6R_7$  (including  $NH_2$ ),  $NR_5COR_6$ ,  $NR_5CONR_6R_7$ ,  $NR_5CO_2R_8$  and  $NR_5SO_2R_8$ , and preferably from  $NR_6R_7$  (including  $NH_2$ ),  $NR_5COR_6$ ,  $NR_5CONR_6R_7$ ,  $NR_5CO_2R_8$  and  $NR_5SO_2R_8$ , more preferably from  $NR_6R_7$  (including  $NH_2$ ), and more preferably from  $NH_2$ .

25

In the compounds of formula (I),  $R_2$  is substituted or unsubstituted heteroaryl attached via an unsaturated carbon atom. Preferably, the heteroaryl group is a 5- or 6- membered monocyclic group.

- 30 Preferably,  $R_2$  is a heteroaryl group which is attached to the pyrimidine ring of formula (I) such that at least one heteroatom is adjacent to the unsaturated carbon atom attached to the pyrimidine ring. Preferably,  $R_2$  is an N, O or S-containing heteroaryl group.  $R_2$  may contain one or more heteroatom(s) selected from N, O and S.

It is preferred that  $R_2$  is not an ortho,ortho-disubstituted heteroaryl group, and preferably  $R_2$  is not substituted at either ortho position. As used herein, reference to ortho-substitution of the  $R_2$  group means the ortho positions of the  $R_2$  group relative to the point of attachment of  $R_2$  to the pyrimidine moiety of formula (I).

In a preferred embodiment,  $R_2$  is selected from furyl (including 2-furyl), thienyl (including 2-thienyl), pyridyl (including 2-pyridyl), thiazolyl (including 2- and 5-thiazolyl), pyrazolyl (including 3-pyrazolyl), triazolyl (including 4-triazolyl), pyrrolyl (including 2-pyrrolyl) and oxazolyl (including 5-oxazolyl). In a further embodiment,  $R_2$  is selected from 2-furyl, 2-thienyl, 2-thiazolyl, 2-pyridyl, 3-pyrazolyl, 2-pyrrolyl, 4-triazolyl and 5-oxazolyl. In a further preferred embodiment,  $R_2$  is selected from furyl, thienyl, pyridyl, thiazolyl and pyrazolyl, and particularly from 2-furyl, 2-thienyl, 2-thiazolyl, 2-pyridyl and 3-pyrazolyl. In a further embodiment,  $R_2$  is selected from furyl, thienyl and pyridyl, preferably 2-furyl, 2-thienyl and 2-pyridyl. In a particularly preferred embodiment,  $R_2$  is selected from furyl, and preferably from 2-furyl, substituted or unsubstituted.

In the compounds of formula (I),  $R_3$  is selected from H, alkyl (including branched and unbranched alkyl, substituted and unsubstituted alkyl, and cyclic and acyclic alkyl), halogen,  $OR_5$ ,  $SR_5$  and  $NR_6R_7$ .

Where  $R_3$  is selected from alkyl, alkoxy and alkylthio, then said alkyl group or the alkyl group of the alkoxy or alkylthio is preferably selected from  $C_{1-6}$  alkyl (including branched and unbranched alkyl, substituted and unsubstituted alkyl, and cyclic and acyclic alkyl), preferably saturated  $C_{1-6}$  alkyl, and more preferably lower alkyl.

Preferably,  $R_3$  is hydrogen.

In the compounds of formula (I),  $R_4$  is selected from H, acyclic alkyl (including branched and unbranched acyclic alkyl, and substituted and unsubstituted acyclic alkyl),  $CONR_6R_7$ ,  $CONR_5NR_6R_7$ ,  $COR_6$ ,  $CO_2R_8$  and  $SO_2R_8$ .

Where  $R_4$  is selected from acyclic alkyl,  $R_4$  is preferably  $C_{1-6}$  acyclic alkyl (including alkenyl and alkynyl). In one embodiment,  $R_4$  is selected from  $C_{1-6}$  saturated acyclic alkyl, preferably lower alkyl.

5

In one embodiment,  $R_4$  is selected from substituted acyclic alkyl (including saturated acyclic alkyl and alkenyl). Preferred substituents are substituted and unsubstituted aryl (including heteroaryl), cycloalkyl, non-aromatic heterocyclyl,  $CO_2R_5$ ,  $CONR_6R_7$ ,  $CONR_5NR_6R_7$  and  $C(=NR_5)NR_6R_7$ , preferably aryl (including heteroaryl) and  $CONR_6R_7$ , more preferably aryl  
10 (including heteroaryl).

Where  $R_4$  is selected from acyclic alkyl substituted by aryl (including heteroaryl), the aryl (including heteroaryl) group may be unsubstituted, or substituted as defined in more detail below in respect of the group referred to as  $R_{11}$ . Preferably, the aryl-substituted acyclic alkyl is an  
15 aryl-substituted methyl group. Preferred aryl groups are set out in detail below in respect of the group referred to as Ar.

In one embodiment,  $R_4$  is selected from  $(CR_9R_{10})_nR_{11}$  wherein  $n$  is 1 to 6 (preferably  $n$  is 1, 2 or 3, more preferably  $n$  is 1),  $R_9$  and  $R_{10}$  are independently selected from H, alkyl and aryl, and  $R_{11}$  is selected from aryl (including heteroaryl), cycloalkyl, non-aromatic heterocyclic,  $CO_2R_5$ ,  
20  $CONR_6R_7$ ,  $CONR_5NR_6R_7$  and  $C(=NR_5)NR_6R_7$ , wherein  $R_{11}$  is preferably aryl (including heteroaryl) or  $CONR_6R_7$ . More preferably  $R_{11}$  is aryl (including heteroaryl). Preferably  $R_9$  and  $R_{10}$  are independently selected from H and alkyl, more preferably H.

Where  $R_{11}$  is selected from  $CONR_6R_7$ ,  $R_6$  and  $R_7$  are selected from H, alkyl (including  
25 substituted alkyl such as arylalkyl (including heteroarylalkyl)) and aryl (including heteroaryl) or  $R_6$  and  $R_7$  may be linked to form a heterocyclic ring. In one embodiment,  $R_6$  and  $R_7$  are selected from H, unsubstituted alkyl, arylalkyl (including heteroarylalkyl) and aryl (including heteroaryl). Said aryl groups may be substituted or unsubstituted. In a preferred embodiment one of  $R_6$  and  $R_7$  is hydrogen.

30

Where  $R_{11}$  is aryl (including heteroaryl), the aryl (including heteroaryl) group may be unsubstituted, or may be substituted. In one embodiment,  $R_{11}$  is selected from the group

consisting of substituted aryl (including heteroaryl) groups, preferably mono-, di- or tri-substituted aryl (including heteroaryl) groups represented by the formula  $\text{Ar}(\text{R}_{12})_a(\text{R}_{13})_b(\text{R}_{14})_c$  wherein Ar is an aryl (including heteroaryl) group; wherein  $\text{R}_{12}$ ,  $\text{R}_{13}$  and  $\text{R}_{14}$  are substituent group(s), the same or different; and wherein a, b and c are 0 or 1 such that  $a+b+c \geq 1$ .

5

In one embodiment, the group Ar is selected from phenyl. In an alternative embodiment, the group Ar is selected from heteroaryl groups such as those described hereinabove, preferably from mono or bicyclic heteroaryl groups, more preferably from pyridyl (including 2-pyridyl, 3-pyridyl and 4-pyridyl, preferably 2-pyridyl), indolyl (including 2-indolyl, 3-indolyl, 4-  
10 indolyl, 5-indolyl, 6-indolyl and 7-indolyl), furyl (including 2-furyl and 3-furyl, preferably 2-furyl), thienyl (including 2-thienyl and 3-thienyl, preferably 2-thienyl), isoindolyl, indolinyl, isoxazolyl, oxazolyl, thiazolyl, pyrazinyl, pyrimidinyl, quinolinyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, indazolyl, benzodioxolyl and dihydrobenzofuranyl, more preferably from pyridyl (preferably 2-pyridyl), indolyl, furyl (preferably 2-furyl) and thienyl  
15 (preferably 2-thienyl), and most preferably from pyridyl (preferably 2-pyridyl), furyl (preferably 2-furyl) and thienyl (preferably 2-thienyl).

In one embodiment, the group Ar is selected from phenyl, pyridyl (preferably 2-pyridyl), furyl (preferably 2-furyl), thienyl (preferably 2-thienyl) and indolyl, and particularly from phenyl,  
20 pyridyl (preferably 2-pyridyl), furyl (preferably 2-furyl) and thienyl (preferably 2-thienyl).

The substituent groups  $\text{R}_{12}$ ,  $\text{R}_{13}$  and  $\text{R}_{14}$  may be selected from any of the substituent groups described herein above.

25 In a preferred embodiment,  $\text{R}_{12}$ ,  $\text{R}_{13}$  and  $\text{R}_{14}$  are selected from  $\text{NR}_6\text{R}_7$  (including  $\text{NH}_2$ , and  $\text{NHR}_6$ ), alkyl (substituted or unsubstituted; preferably  $\text{C}_{1-6}$  acyclic alkyl), alkoxy (including fluoroalkoxy), halogen (including F, Cl, Br and I),  $\text{NO}_2$ , CN, hydroxy,  $\text{NHOH}$ , CHO,  $\text{CONR}_6\text{R}_7$ ,  $\text{CO}_2\text{R}_5$ ,  $\text{NR}_5\text{COR}_6$  (preferably  $\text{NHCOR}_6$ ),  $\text{NR}_5\text{CO}_2\text{R}_8$  (preferably  $\text{NHCO}_2\text{R}_8$ ),  $\text{NR}_5\text{SO}_2\text{R}_8$  (preferably  $\text{NHSO}_2\text{R}_8$ ),  $\text{OCO}_2\text{R}_8$  and aryl (including heteroaryl).

30

In a more preferred embodiment,  $\text{R}_{12}$ ,  $\text{R}_{13}$  and  $\text{R}_{14}$  are selected from  $\text{NR}_6\text{R}_7$  (including  $\text{NH}_2$  and  $\text{NHR}_6$ ), alkyl (substituted or unsubstituted; and preferably  $\text{C}_{1-6}$  acyclic saturated alkyl) and halogen (preferably F or Cl, particularly F).



In a particularly preferred embodiment,  $R_{12}$ ,  $R_{13}$  and  $R_{14}$  are selected from  $NR_6R_7$  (including  $NH_2$  and  $NHR_6$ , preferably  $NH_2$ ) and alkyl (substituted or unsubstituted; preferably  $C_{1-6}$  acyclic saturated alkyl;

5

Where  $R_{12}$ ,  $R_{13}$  and  $R_{14}$  are selected from substituted alkyl, said alkyl is preferably selected from alkoxyalkyl, hydroxyalkyl, aminoalkyl (including  $NH_2$ -alkyl, mono-alkylaminoalkyl and di-alkylaminoalkyl), haloalkyl (particularly fluoroalkyl (including  $CF_3$ )), cyanoalkyl, alkylthioalkyl, alkylcarboxyaminoalkyl, alkoxycarbonylaminoalkyl and alkylsulfonylamino, 10 more preferably from alkoxyalkyl, hydroxyalkyl, aminoalkyl and haloalkyl (particularly fluoroalkyl (including  $CF_3$ )) and most preferably from alkoxyalkyl and aminoalkyl.

In one embodiment, the substituent groups  $R_{12}$ ,  $R_{13}$  and  $R_{14}$  are selected from halogen, alkyl (including  $CF_3$ ), hydroxy, alkoxy, alkylthio, CN, amines (including amino, mono- and di-alkyl 15 amino) and  $NO_2$ .

Where the Ar group is phenyl, the phenyl ring may be mono-, di- or tri-substituted, preferably wherein the substituent group is selected from  $NR_6R_7$ , alkyl, alkoxy, halogen,  $NO_2$ , CN, hydroxy,  $CONR_6R_7$ ,  $CO_2R_5$ ,  $NR_5COR_6$ ,  $NR_5CO_2R_8$ ,  $NR_5SO_2R_8$  and  $OCO_2R_8$ , as described 20 above, and more preferably from  $NR_6R_7$  (including  $NH_2$  and  $NHR_6$ , and preferably  $NH_2$ ), alkyl (substituted or unsubstituted; preferably  $C_{1-6}$  acyclic saturated alkyl; and, where substituted, preferably from alkoxyalkyl, hydroxyalkyl, aminoalkyl and haloalkyl (particularly fluoroalkyl (including  $CF_3$ )), and more preferably from alkoxyalkyl and aminoalkyl) and halogen (preferably F or Cl, particularly F). Where  $(a+b+c)$  is 2 or 3, it is preferred that at 25 least one of the substituent groups is  $NR_6R_7$ , particularly  $NH_2$ .

Where the Ar group is pyridyl, the pyridyl group (which is preferably a 2-pyridyl group) is preferably mono-substituted, preferably 6-substituted. The preferred substituent group(s) are selected from alkyl (including substituted and unsubstituted, saturated and unsaturated (such as 30 alkenyl, including vinyl); and preferably  $C_{1-6}$  acyclic alkyl), alkoxy, halogen, aryl,  $NO_2$ ,  $NHOH$  and  $CHO$ , as described above, and more preferably from alkyl (substituted or unsubstituted; preferably  $C_{1-6}$  acyclic saturated alkyl; and, where substituted, preferably from

alkoxyalkyl, hydroxyalkyl, aminoalkyl and haloalkyl (particularly fluoroalkyl (including  $\text{CF}_3$ )), and more preferably from alkoxyalkyl and aminoalkyl).

- 5 Where  $R_4$  is selected from  $\text{CONR}_6\text{R}_7$ ,  $R_6$  and  $R_7$  are selected from H, alkyl (including substituted alkyl such as arylalkyl (including heteroarylalkyl)) and aryl (including heteroaryl) or  $R_6$  and  $R_7$  may be linked to form a heterocyclic ring. In one embodiment,  $R_6$  and  $R_7$  are selected from H, unsubstituted alkyl, arylalkyl (including heteroarylalkyl) and aryl (including heteroaryl). Said aryl groups may be substituted or unsubstituted. In a preferred embodiment
- 10 one of  $R_6$  and  $R_7$  is hydrogen. In a further preferred embodiment,  $R_6$  is H and  $R_7$  is selected from arylalkyl (including heteroarylalkyl), preferably arylmethyl (including heteroarylmethyl).

In a preferred embodiment,  $R_4$  is selected from H and substituted acyclic alkyl, preferably wherein said acyclic alkyl is substituted by aryl (including heteroaryl) or  $\text{CONR}_6\text{R}_7$ , and

15 preferably by aryl (including heteroaryl), as described herein.

In the compounds of formula (I),  $R_5$ ,  $R_6$  and  $R_7$  are independently selected from H, alkyl (including branched and unbranched alkyl, substituted and unsubstituted alkyl, cyclic and acyclic alkyl) and aryl (including heteroaryl) or where  $R_6$  and  $R_7$  are in any  $\text{NR}_6\text{R}_7$  group  $R_6$

20 and  $R_7$  may be linked to form a heterocyclic group, or where  $R_5$ ,  $R_6$  and  $R_7$  are in a  $(\text{CONR}_5\text{NR}_6\text{R}_7)$  group,  $R_5$  and  $R_6$  may be linked to form a heterocyclic group.

In the compounds of formula (I),  $R_8$  is selected from alkyl (including branched and unbranched alkyl, substituted and unsubstituted alkyl, cyclic and acyclic alkyl) and aryl

25 (including heteroaryl).

Where  $R_5$  to  $R_8$  are independently selected from alkyl, preferably  $R_5$  to  $R_8$  are selected from  $\text{C}_{1-6}$  alkyl, preferably  $\text{C}_{1-6}$  saturated alkyl and more preferably from lower alkyl.

- 30 Where  $R_6$  and  $R_7$ , or  $R_5$  and  $R_6$ , are linked to form a heterocyclic ring said heterocyclic ring may be saturated, partially unsaturated or aromatic, and is preferably saturated. Said heterocyclic ring is preferably a 5, 6 or 7-membered ring, preferably a 5 or 6-membered ring, and may contain one or more further heteroatom(s) preferably selected from N, O and S.

In a preferred embodiment, R<sub>1</sub> is NH<sub>2</sub>, R<sub>2</sub> is 2-furyl, R<sub>3</sub> is H and R<sub>4</sub> is arylmethyl (including heteroarylmethyl).

- 5 In a particularly preferred embodiment of the invention, the compounds of formula (I) are selected from:
- 4-(2-furyl)-1-(3-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine;
  - 1-(2-fluorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine;
  - 4-(2-furyl)-1-(3-methylbenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine;
  - 10 1-(2,6-difluorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine;
  - 4-(2-furyl)-1-(3-phenylpropyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine; and
  - 1-(2-fluorobenzyl)-4-(2-pyridyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine.

Where chiral the compounds of formula (I) may be in the form of a racemic mixture of pairs  
15 of enantiomers or in enantiomerically pure form.

According to a further aspect of the present invention there is provided a method of treating or preventing a disorder in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A<sub>2A</sub> receptors, may be beneficial, the method  
20 comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof.

The disorder may be caused by the hyperfunctioning of the purine receptors.

25 The present invention may be employed in respect of a human or animal subject, more preferably a mammal, more preferably a human subject.

The disorders of particular interest are those in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A<sub>2A</sub> receptors, may be  
30 beneficial. These may include movement disorders such as Parkinson's disease, drug-induced Parkinsonism, post-encephalitic Parkinsonism, Parkinsonism induced by poisoning (for example MPTP, manganese, carbon monoxide) and post-traumatic Parkinson's disease (punch-drunk syndrome).

- Other movement disorders in which the blocking of purine receptors, may be of benefit include progressive supranuclear palsy, Huntingtons disease, multiple system atrophy, corticobasal degeneration, Wilsons disease, Hallerorden-Spatz disease, progressive pallidal atrophy, Dopa-responsive dystonia-Parkinsonism, spasticity or other disorders of the basal ganglia which result in abnormal movement or posture. The present invention may also be effective in treating Parkinson's with on-off phenomena; Parkinson's with freezing (end of dose deterioration); and Parkinson's with prominent dyskinesias.
- 10 The compounds of formula (I) may be used or administered in combination with one or more additional drugs useful in the treatment of movement disorders, such as L-DOPA or a dopamine agonist, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.
- 15 Other disorders in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine  $A_{2A}$  receptors may be beneficial include acute and chronic pain; for example neuropathic pain, cancer pain, trigeminal neuralgia, migraine and other conditions associated with cephalic pain, primary and secondary hyperalgesia, inflammatory pain, nociceptive pain, tabes dorsalis, phantom limb pain, spinal cord injury
- 20 pain, central pain, post-herpetic pain and HIV pain; affective disorders including mood disorders such as bipolar disorder, seasonal affective disorder, depression, manic depression, atypical depression and monodepressive disease; central and peripheral nervous system degenerative disorders including corticobasal degeneration, demyelinating disease (multiple sclerosis, disseminated sclerosis), Freidrich's ataxia, motoneurone disease
- 25 (amyotrophic lateral sclerosis, progressive bulbar atrophy), multiple system atrophy, myelopathy, radiculopathy, peripheral neuropathy (diabetic neuropathy, tabes dorsalis, drug-induced neuropathy, vitamin deficiency), systemic lupus erythamatosi, granulomatous disease, olivo-ponto-cerebellar atrophy, progressive pallidal atrophy, progressive supranuclear palsy, spasticity; schizophrenia and related psychoses; cognitive
- 30 disorders including dementia, Alzheimers Disease, Frontotemporal dementia, multi-infarct dementia, AIDS dementia, dementia associated with Huntingtons Disease, Lewy body dementia, senile dementia, age-related memory impairment, cognitive impairment associated with dementia, Korsakoff syndrome, dementia pugilans; attention disorders such

as attention-deficit hyperactivity disorder (ADHD), attention deficit disorder, minimal brain dysfunction, brain-injured child syndrome, hyperkinetic reaction childhood, and hyperactive child syndrome; central nervous system injury including traumatic brain injury, neurosurgery (surgical trauma), neuroprotection for head injury, raised intracranial  
5 pressure, cerebral oedema, hydrocephalus, spinal cord injury; cerebral ischaemia including transient ischaemic attack, stroke (thrombotic stroke, ischaemic stroke, embolic stroke, haemorrhagic stroke, lacunar stroke) subarachnoid haemorrhage, cerebral vasospasm, neuroprotection for stroke, peri-natal asphyxia, drowning, cardiac arrest, subdural haematoma; myocardial ischaemia; muscle ischaemia; sleep disorders such as hypersomnia  
10 and narcolepsy; eye disorders such as retinal ischaemia-reperfusion injury and diabetic neuropathy; cardiovascular disorders such as claudication and hypotension; and diabetes and its complications.

According to a further aspect of the present invention there is provided use of a compound  
15 of formula (I) or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for the treatment or prevention of movement disorders in a subject.

According to a further aspect of the invention there is provided a method of treating or preventing movement disorders comprising administration to a subject in need of such  
20 treatment an effective dose of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof.

According to a further aspect of the invention there is provided use of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a  
25 medicament for neuroprotection in a subject.

According to a further aspect of the invention there is provided a method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof.

30

The medicament for or method of neuroprotection may be of use in the treatment of subjects who are suffering from or at risk from a neurodegenerative disorder, such as a movement disorder.

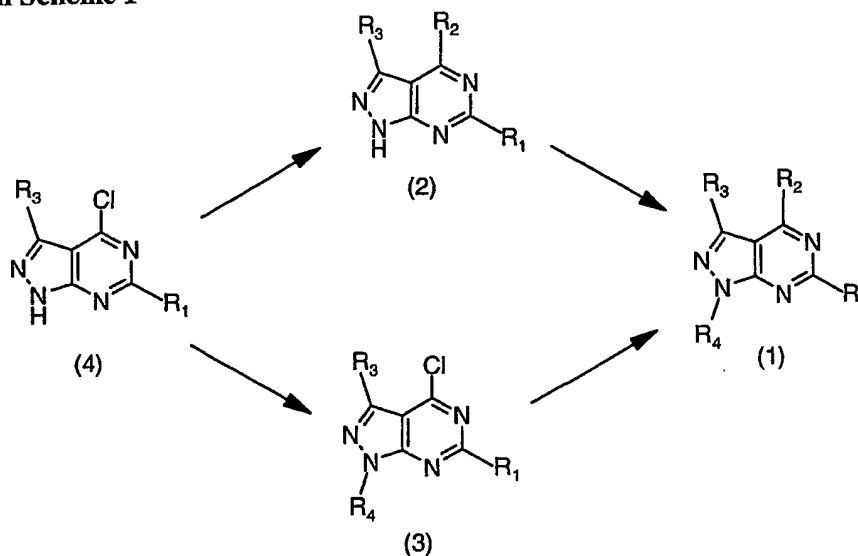
According to a further aspect of the invention, there is provided for use in therapy a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

- 5 According to a further aspect of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, *per se*, other than compounds wherein  $R_2$  is selected from pyrazolopyrimidines. In a preferred embodiment, there is provided a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, *per se*, wherein  $R_2$  is selected from 5- or 6- membered monocyclic heteroaryl groups.

According to a further aspect of the invention, there is provided a method of preparing the novel compounds of the present invention. Compounds of formula (I) may be prepared according to conventional synthetic methods, such as set out in Reaction Scheme 1.

15

#### Reaction Scheme 1



- Compounds of formula (1) where  $R_4$  is alkyl or substituted alkyl (including arylalkyl, heteroalkylaryl and  $(CR_9R_{10})_nR_{11}$  wherein  $R_{11}$  is  $CO_2R_5$  or  $CN$ ) may be prepared from compounds of formula (2) by standard methods such as reaction with an appropriate alkyl halide or substituted alkyl halide in the presence of a suitable base such as NaH.

Compounds of formula (1) where  $R_4$  is  $(CR_9R_{10})_nR_{11}$  wherein  $R_{11}$  is  $CONR_6R_7$  or  $CONR_5NR_6R_7$  may be prepared from compounds of formula (1) where  $R_4$  is  $(CR_9R_{10})_nR_{11}$  wherein  $R_{11}$  is  $CO_2R_5$  by standard methods such as direct reaction with an appropriate amine or hydrazine derivative or by initial hydrolysis of the ester group  $CO_2R_5$  to a  
5 carboxylic acid followed by reaction with an appropriate amine or hydrazine derivative in the presence of a standard coupling reagent such as DCC.

Compounds of formula (1) where  $R_4$  is  $(CR_9R_{10})_nR_{11}$  wherein  $R_{11}$  is  $C(=NR_5)NR_6R_7$  may be prepared from compounds of formula (1) where  $R_4$  is  $(CR_9R_{10})_nR_{11}$  wherein  $R_{11}$  is CN  
10 by standard methods such as treatment with an appropriate amine in the presence of trimethylaluminium.

Compounds of formula (1) where  $R_4$  is  $CONR_6R_7$ , wherein one of  $R_6$  or  $R_7$  is H, are prepared from compounds of formula (2) by standard methods such as reaction with an  
15 appropriate isocyanate ( $R_6NCO$  or  $R_7NCO$ ). Compounds of formula (1) where  $R_4$  is  $CONR_6R_7$ , wherein  $R_6$  and  $R_7$  are alkyl or aryl or are linked to form a heterocyclic group, are prepared from compounds of formula (2) by standard methods such as reaction with an appropriate carbamoyl chloride ( $R_6R_7NCOCl$ ) in the presence of a suitable base such as  $Et_3N$ .

20

Compounds of formula (1) wherein  $R_4$  is  $CONR_5NR_6R_7$  are prepared from compounds of formula (2) by standard methods such as reaction with an appropriate carbamoyl chloride  $R_6R_7NR_5NCOCl$  in the presence of a suitable base such as  $Et_3N$ .

25 Compounds of formula (1) where  $R_4$  is  $COR_6$  or  $SO_2R_8$  are prepared from compounds of formula (2) by standard methods such as reaction with an appropriate acid chloride ( $ClCOR_6$ ) or sulphonyl chloride ( $ClSO_2R_8$ ) in the presence of a suitable base such as  $Et_3N$ .

Compounds of formula (1) where  $R_4$  is  $CO_2R_8$  are prepared from compounds of formula (2)  
30 by standard methods such as reaction with an appropriate chloroformate ( $ClCO_2R_8$ ) or dicarbonate ( $O(CO_2R_8)_2$ ) in the presence of a suitable base, if required, such as  $Et_3N$  and in the presence of a suitable catalyst, if required, such as DMAP.

Alternatively compounds of formula (1) are prepared from compounds of formula (3) by standard methods such as aryl coupling reactions. Suitable aryl coupling reactions would include reaction of a compound of formula (3) with a heteroaryl trialkylstannane, a heteroarylboronic acid or boronic ester, or a heteroaryl zinc halide reagent in the presence  
5 of a suitable catalyst such as a palladium catalyst. Suitable heteroaryl trialkylstannane, heteroarylboronic acid or boronic ester, or heteroaryl zinc halide reagents are either commercially available, known in the literature or may be synthesised by standard methods analogous to those described in the literature. In certain cases it may be advantageous to use a protecting group to protect vulnerable functionality which may be present in the  
10 heteroaryl coupling partner. This would be particularly appropriate where the heteroaryl group  $R_2$  is imidazolyl, pyrazolyl or triazolyl where protection of an unsubstituted ring nitrogen may be necessary to facilitate the coupling reaction. Suitable protecting groups in such cases would include trimethylsilylethoxymethyl which can be introduced and removed at a convenient point in the synthesis by standard methods.

15

Compounds of formula (2) are prepared from compounds of formula (4) by standard methods such as aryl coupling reactions as described above. Compounds of formula (4) where  $R_1$  is alkyl, aryl, alkylthio, halogen and  $NR_6R_7$  are either known in the literature or are prepared by methods analogous to those described in the literature.

20

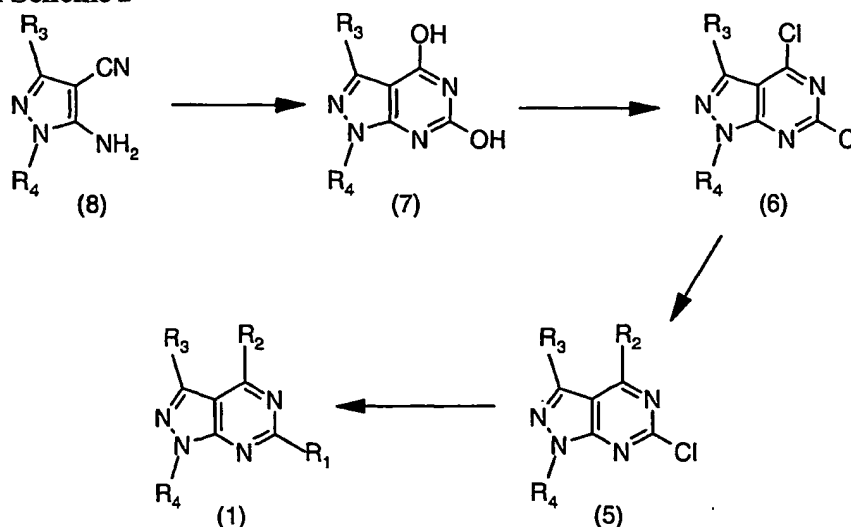
Compounds of formula (3) are prepared from compounds of formula (4) by standard methods such as those described above. Compounds of formula (3) where  $R_1$  is alkyl, aryl, alkylthio, halogen or  $NR_6R_7$  are either known in the literature or may be prepared by methods analogous to those described in the literature.

25

Compounds of formula (1) may alternatively be prepared by standard synthetic methods such as those illustrated in Reaction Scheme 2.



## Reaction Scheme 2



Compounds of formula (1) where  $R_1$  is  $NR_6R_7$ , alkoxy, aryloxy, alkylthio, arylthio or CN are prepared from compounds of formula (5) by standard methods such as treatment with an appropriate nucleophile such as an amine ( $HNR_6R_7$ ), alcohol, thiol or cyanide in the presence of a suitable base if required.

Compounds of formula (5) are prepared from compounds of formula (6) by standard methods such as aryl coupling reactions as described above.

Compounds of formula (6) are either known in the literature or are prepared by methods analogous to those described in the literature. For example compounds of formula (6) are prepared from compounds of formula (7) by standard methods such as treatment with a chlorinating reagent such as  $POCl_3$ .

Compounds of formula (7) are either known in the literature or are prepared by methods analogous to those described in the literature. For example compounds of formula (7) are prepared from compounds of formula (8) by standard methods such as heating in the presence of urea. Compounds of formula (8) are either known in the literature or are prepared by methods analogous to those described in the literature.

Compounds of formula (1) where  $R_1$  is  $NR_5COR_6$ ,  $NR_5CO_2R_8$  or  $NR_5SO_2R_8$  wherein  $R_5$  is H, alkyl or aryl, are prepared from compounds of formula (1) where  $R_1$  is  $NR_6R_7$ , wherein

one of  $R_6$  or  $R_7$  is H and the other is alkyl or aryl, by standard methods such as reaction with an appropriate acid chloride ( $ClCOR_6$ ), chloroformate ( $ClCO_2R_8$ ) or sulphonyl chloride ( $ClSO_2R_8$ ).

- 5 Compounds of formula (1) where  $R_1$  is  $NR_5CONR_6R_7$  wherein  $R_5$  is H, alkyl or aryl, are prepared from compounds of formula (1) where  $R_1$  is  $NR_6R_7$ , wherein one of  $R_6$  or  $R_7$  is H and the other is alkyl or aryl, by standard methods such as reaction with an appropriate isocyanate ( $R_6NCO$  or  $R_7NCO$ ) or an appropriate carbamoyl chloride ( $R_6R_7NCOCI$ ).
- 10 Compounds of formula (1) where  $R_3$  is H, alkyl, halogen,  $OR_5$ ,  $SR_5$  or  $NR_6R_7$  may be prepared by the methods described above. Suitable intermediates such as compounds of formula (3) and (4) where  $R_3$  is as described above, are either known in the literature or are prepared by methods which are analogous to those described in the literature.
- 15 In the compounds of the present invention, where any of the groups  $R_1$  to  $R_8$  is an alkyl group or aryl group or where any of the groups  $R_1$  to  $R_8$  contains an alkyl or aryl substituent, the alkyl or aryl group may also be substituted. It will be appreciated by those skilled in the art that certain substituents on the alkyl or aryl groups mentioned above may be introduced directly as an integral part of the substituent  $R_1$  to  $R_8$  by using the synthetic
- 20 methods described above. In other cases it may be advantageous to introduce certain substituents on the alkyl or aryl groups mentioned above by chemical transformation of other substituent groups. For example where the alkyl or aryl group mentioned above contains an amino substituent this may be converted by standard methods to an alkylamino or dialkylamino group by standard methods such as alkylation or reductive alkylation, or to
- 25 an amide, carbamate, urea or sulphonamide by standard methods such as those described above. Additionally, for example, where the alkyl or aryl group mentioned above contains a carboxylic ester substituent this may be converted to an amide or hydrazide derivative by standard methods such as reaction with an amine or hydrazine directly or in the presence of a catalyst such as  $Me_3Al$  if required. It will be appreciated by those skilled in the art that
- 30 substituents such as an amino group or a carboxylic ester group may also be transformed by standard methods to a wide range of additional substituent groups.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or  
5 excipient.

The pharmaceutical compositions employed in the present invention comprise a compound of formula (I), or pharmaceutically acceptable salts or prodrugs thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients  
10 known to those skilled in the art. The term, "pharmaceutically acceptable salts", refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

Where the compounds of formula (I) are basic, salts may be prepared from  
15 pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are  
20 hydrochloric, hydrobromic, phosphoric, and sulfuric acids, and most particularly preferred is the hydrochloride salt.

Any suitable route of administration may be employed for providing the patient with an effective dosage of a compound of formula (I). For example, oral, rectal, parenteral  
25 (intravenous, intramuscular), transdermal, subcutaneous, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like. The most suitable route in any given case will depend on the severity of the condition being treated. The most preferred route of administration of the present invention is the oral route. The compositions may be conveniently presented in unit dosage  
30 form and prepared by any of the methods well known in the art of pharmacy.

In practical use, the compounds of formula (I) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical

compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.* oral or parenteral (*e.g.* intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavouring  
5 agents, preservatives, colouring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used in the case of oral solid preparations such as, for example, powders, capsules, and tablets, with the solid oral preparations being preferred over the  
10 liquid preparations. The most preferred solid oral preparation is tablets.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or non-aqueous  
15 techniques.

In addition to the common dosage forms set out above, the compounds of formula (I) may also be administered by controlled release means and/or delivery devices such as those described in United States Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123;  
20 3,630,200; 4,008,719; 4,687,660; and 4,769,027, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions employed in the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or  
25 aerosol sprays each containing a predetermined amount of the active ingredient as a powder or granules, a solution or a suspension in an aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more necessary ingredients. In general, the  
30 compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, a lubricant, an inert diluent, and/or a surface active or  
 5 dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The invention is further defined by reference to the following examples. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be  
 10 practised without departing from the purpose and interest of this invention.

## EXAMPLES

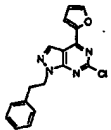
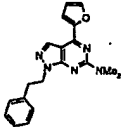
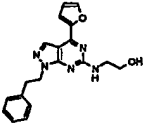
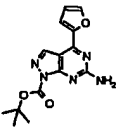
### Synthetic Examples

15

The invention is illustrated with reference to the following Examples, as set out in Table 1. The synthesis of these compounds is performed using the general Synthetic Methods A to Q described hereinafter. The Synthetic Method used for the preparation of each Example is given in parentheses in column 1 of Table 1. Analytical data are given in Table 2.

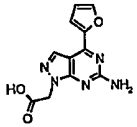
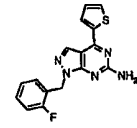
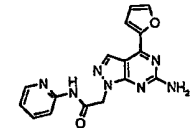
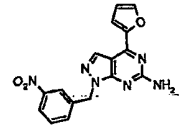
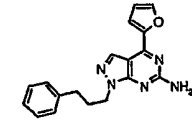
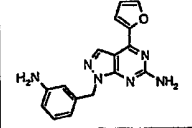
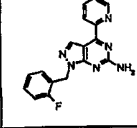
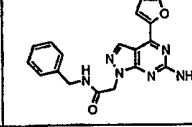
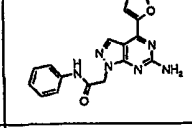
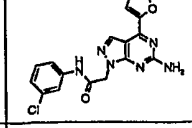
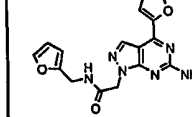
20

**Table 1**

Example	Structure	Compound Name
1 (B)		6-chloro-4-(2-furyl)-1-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine
2 (N)		4-(2-furyl)-N,N-dimethyl-1-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
3 (O)		4-(2-furyl)-N-(2-hydroxyethyl)-1-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
4 (B)		<i>tert</i> -butyl 6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-carboxylate

5 (C)		4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
6 (P)		6-amino-N-benzyl-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-carboxamide
7 (D)		1-benzyl-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
8 (D)		1-(3-chlorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
9 (D)		4-(2-furyl)-1-(4-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
10 (D)		1-(3-cyanobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
11 (D)		1-(2-chlorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
12 (D)		4-(2-furyl)-1-(3-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
13 (D)		4-(2-furyl)-1,N,N-tris(3-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
14 (D)		1-(2-fluorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
15 (D)		4-(2-furyl)-1-(3-methylbenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine

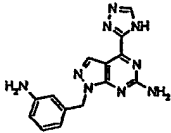
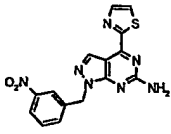
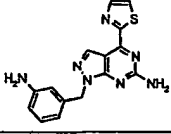
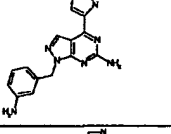
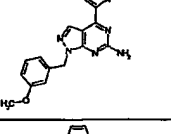
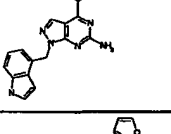
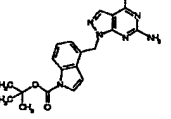
16 (D)		methyl 3-(6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylmethyl)benzoate
17 (D)		4-(2-furyl)-1-(4-sulphonylbenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
18 (D)		4-(2-furyl)-1-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
19 (D)		1-cyclohexylmethyl-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
20 (G)		3-(6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylmethyl)benzoic acid
21 (D)		4-(2-furyl)-1-(1-methylethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
22 (D)		4-(2-furyl)-1-(4-trifluoromethylbenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
23 (D)		4-(2-furyl)-1-n-pentyl-1H-pyrazolo[3,4-d]pyrimidine-6-amine
24 (D)		1-(2,6-difluorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
25 (D)		4-(2-furyl)-1-(3-pyridylmethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
26 (D)		ethyl 6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetate

27 (G)		6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetic acid
28 (I)		1-(2-fluorobenzyl)-4-(2-thienyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
29 (H)		6-amino-4-(2-furyl)-N-(2-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide
30 (D)		4-(2-furyl)-1-(3-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
31 (D)		4-(2-furyl)-1-(3-phenylpropyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
32 (E)		1-(3-aminobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
33 (J)		1-(2-fluorobenzyl)-4-(2-pyridyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
34 (H)		6-amino-N-benzyl-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide
35 (H)		6-amino-4-(2-furyl)-N-phenyl-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide
36 (H)		6-amino-N-(3-chlorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide
37 (H)		6-amino-4-(2-furyl)-N-(2-furylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide



38 (J)		1-(2-fluorobenzyl)-4-(2-thiazolyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
39 (D)		4-(2-furyl)-1-(2-furylmethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
40 (F)		4-(2-furyl)-1-(4-methylphenylsulphonyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
41 (J)		1-(2-fluorobenzyl)-4-(1-methyl-2-imidazolyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
42 (K)		1-(2-fluorobenzyl)-4-(2-imidazolyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
43 (H)		6-amino-4-(2-furyl)-N-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide
44 (H)		6-amino-4-(2-furyl)-N-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide
45 (H)		6-amino-N-(2-fluorophenyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide
46 (D)		3-(6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylmethyl)-N-methylbenzamide
47 (D)		3-(6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylmethyl)-N,N-dimethylbenzamide
48 (H)		6-amino-4-(2-furyl)-N-(2-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide

49 (H)		6-amino-N-(2-fluorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide
50 (K)		1-(4-methylbenzyl)-4-(1H-pyrazol-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
51 (K)		1-(2-fluorobenzyl)-4-(1,2,4-triazol-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
52 (D)		4-(2-furyl)-1-(2-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
53 (F)		N-(4-(2-furyl)-1-(3-(2-thiophenesulphonamido)benzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-yl)-2-thiophenesulphonamide
54 (F)		N-((3-(6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-ylmethyl)phenyl)-2-thiophenesulphonamide
55 (K)		1-(2-fluorobenzyl)-4-(3-pyrazolyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
56 (E)		1-(2-aminobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
57 (F)		N-((3-(6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-ylmethyl)phenyl)-1-methyl-1H-imidazol-4-sulphonamide
58 (K)		1-(3-nitrobenzyl)-4-(1,2,4-triazol-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
59 (K)		1-(3-nitrobenzyl)-4-(3-pyrazolyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine

60 (E)		1-(3-aminobenzyl)-4-(1,2,4-triazol-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
61 (J)		1-(3-nitrobenzyl)-4-(2-thiazolyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
62 (E)		1-(3-aminobenzyl)-4-(2-thiazolyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
63 (E)		1-(3-aminobenzyl)-4-(1H-pyrazol-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
64 (K)		1-(3-methoxybenzyl)-4-(1H-pyrazol-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
65 (Q)		4-(2-furyl)-1-(4-indolylmethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine
66 (D)		<i>tert</i> -butyl 4-(6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-ylmethyl)indole-1-carboxylate

### Synthetic Methods

#### 5 Method A

##### ***tert*-Butyl 6-amino-4-chloro-1H-pyrazolo[3,4-d]pyrimidine-1-carboxylate**

A solution of 2-amino-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (848 mg, 5 mmol) in DMF (5 mL) was treated with Et<sub>3</sub>N (834  $\mu$ L, 6 mmol), di-*t*-butyl dicarbonate (1.31 g, 6 mmol) and a catalytic amount of DMAP, stirred at room temperature for 1 h, poured into water, extracted with EtOAc, dried (MgSO<sub>4</sub>), concentrated *in vacuo* and purified by chromatography (EtOAc : Heptane, 1:1) to give the *title compound* (312 mg, 23 %) as a cream solid.

**Method B*****tert*-Butyl 6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-carboxylate (Example 4)**

A solution of *tert*-butyl 6-amino-4-chloro-1H-pyrazolo[3,4-d]pyrimidine-1-carboxylate (269 mg, 1 mmol) in DMF (2 mL) was treated with PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (35 mg, 0.05 mmol) and 2-(tributylstannyl)furan (315 µL, 1 mmol), stirred at room temperature for 16 h and the resulting solid filtered and washed with EtOAc to give the *title compound* (298 mg, 99 %) as a cream solid.

**10 Method C****4-(2-Furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (Example 5)**

A solution of *tert*-butyl 6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-carboxylate (204 mg, 0.68 mmol) in MeOH (2 mL) was treated with dimethylamine in water (0.5 mL, 40 %), refluxed for 1 h, cooled and the resulting solid filtered and washed with water to give the *title compound* (95 mg, 70 %) as a cream solid.

**Method D****1-(2-Fluorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (Example 14)**

A solution of 4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (219 mg, 1 mmol) in DMF (2 mL) at 0 °C was treated with NaH (40 mg, 60 %, 1 mmol), stirred for 20 min, treated with 2-fluorobenzyl bromide (120 µL, 1 mmol), stirred at room temperature for 1 h, quenched with water, extracted with EtOAc, dried (MgSO<sub>4</sub>), concentrated *in vacuo* and purified by chromatography (EtOAc : Heptane, 1:4) to give the *title compound* (250 mg, 76 %) as a cream solid.

25

**4-(2-Furyl)-1-(3-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (Example 30)**

A solution of 4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (603 mg, 3 mmol) in DMF (3 mL) at 0 °C was treated with NaH (120 mg, 60 %, 3 mmol), stirred for 20 min, treated with 3-nitrobenzyl bromide (648 mg, 3 mmol), stirred at room temperature for 1 h, poured into water, extracted with EtOAc, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The crude product was purified by chromatography (EtOAc : Heptane, 1:1) to give the *title compound* as a cream solid (472 mg, 47 %). A portion of the solid (70 mg) was suspended in MeOH, treated with HCl in dioxan (4-M, 1 mL), diluted with diethyl ether and filtered to give the hydrochloride salt of the *title compound* (79 mg, 100 %) as a yellow solid.

30

**4-Chloro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine**

This was prepared from 4-chloro-1H-pyrazolo[3,4-d]pyrimidine-6-amine by Method D to give the *title compound* (562 mg, 34 %) as a cream solid: mp 197 - 198 °C; NMR  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 5.23 (1H, br s), 5.51 (2H, s), 7.03-7.16 (3H, m), 7.23-7.31 (1H, m) and 7.91 (1H, s); IR  $\nu_{max}$  (Nujol)/cm<sup>-1</sup> 3489, 3288, 3169, 2923, 1631, 1454, 1378, 1223 and 760; Retention time : 2.60 min.

**4-Chloro-1-(3-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine**

10 This was prepared from 4-chloro-1H-pyrazolo[3,4-d]pyrimidine-6-amine by Method D to give the *title compound*: IR  $\nu_{max}$  (DR)/cm<sup>-1</sup> 3435, 3321, 3217, 2923, 1603, 1456, 1378, 1254, 1155, 1034, 980 and 788; NMR  $\delta_H$  (400 MHz, DMSO) 8.03 (1H, s), 7.32 (2H, br s), 7.22 (1H, t, *J* 7.5 Hz), 6.84 (1H, dd, *J* 9.0, 3.5 Hz), 6.79 - 6.75 (1H, m), 6.71 (1H, d, *J* 8.5 Hz), 5.36 (2H, s) and 3.71 (3H, s).

15

**Method E****1-(3-Aminobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (Example 32)**

A suspension of 4-(2-furyl)-1-(3-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (396 mg, 1.18 mmol) in EtOH (5 mL) was heated to 50 °C, treated with a solution of 20 SnCl<sub>2</sub>·2H<sub>2</sub>O (798 mg, 3.54 mmol) in conc. HCl (1.8 mL), stirred at 50 °C for 2 h then heated at 70 °C for 2 h. The reaction mixture was cooled, basified (5-M NaOH) filtered and the resulting solid suspended in MeOH, treated with HCl in dioxan (4-M, 2 mL), diluted with diethyl ether and filtered to give the *title compound* (419 mg, 94 %) as a yellow solid.

25 **Method F****N-((3-(6-Amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-ylmethyl)phenyl-2-thiophenesulphonamide (Example 54)**

A solution of 1-(3-aminobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (153 mg, 0.5 mmol) in pyridine (2 mL) was treated with 2-thiophenesulphonyl chloride (91 mg, 0.5 mmol), stirred at room temperature for 16 h, poured into water, extracted with EtOAc, 30 dried (MgSO<sub>4</sub>), concentrated *in vacuo* and purified by chromatography (MeOH : DCM, 1:99) to give the *title compound* (49 mg, 22 %) as a cream solid.

**Method G****6-Amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetic acid (Example 27)**

A solution of ethyl 6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetate (350 mg, 1.22 mmol) in MeOH (2 mL) was treated with NaOH (1-M, 1 mL, 1 mmol), refluxed for 15 min, cooled, acidified and filtered to give the *title compound* (300 mg, 95 %) as a white solid.

**Method H****6-Amino-4-(2-furyl)-N-(2-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetamide****10 (Example 29)**

A solution of 6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidin-1-ylacetic acid (200 mg, 0.77 mmol) in DMF (3 mL) was treated with carbonyl diimidazole (125 mg, 0.77 mmol), stirred at room temperature for 2 h, treated with 2-aminopyridine (72 mg, 0.77 mmol), heated to 50 °C for 3 h, cooled and diluted with water. The resulting white solid was filtered, suspended in MeOH, treated with HCl in dioxan (4-M, 1 mL) diluted with diethyl ether and filtered to give the *title compound* (187 mg, 59 %) as a yellow solid.

**Method I****1-(2-Fluorobenzyl)-4-(2-thienyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (Example 28)**

20 A stirred solution of 4-chloro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (139 mg, 0.5 mmol) in dry THF (10 mL) was treated with 2-thiopheneboronic acid (128 mg, 1.0 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (50 mg, 10 mol%) and saturated aqueous NaHCO<sub>3</sub> solution (2 mL), refluxed for 30 min, diluted with H<sub>2</sub>O, extracted with EtOAc, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The resulting dark brown oil was purified by chromatography [SiO<sub>2</sub>; 25 heptane:EtOAc (1:1) then (1:3)] to give the *title compound* (32 mg, 20 %) as a cream solid.

**Method J****1-(2-Fluorobenzyl)-4-(2-thiazolyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (Example 38)**

30 A stirred solution of thiazole (0.14 mL, 2 mmol) in dry THF (10 mL) at -78 °C, under argon was treated n-BuLi (1.6-M in hexanes, 1.25 mL, 2 mmol), stirred for 15 min, treated with ZnCl<sub>2</sub> solution (1-M in Et<sub>2</sub>O, 2 mL, 2 mmol) then allowed to warm gradually to room temperature. The mixture was treated with 4-chloro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-

d]pyrimidine-6-amine (278 mg, 1 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (100 mg, 10 mol%), refluxed for 2 h, diluted with saturated NH<sub>4</sub>Cl solution, extracted with EtOAc, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The resulting brown oil was purified by chromatography [SiO<sub>2</sub>; heptane:EtOAc (4:1) then (3:1)] to give the *title compound* (101 mg, 31 %) as a cream solid.

5

#### Method K

##### **1-(2-Fluorobenzyl)-4-(3-pyrazolyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (Example 55)**

A stirred solution of 1-(2-trimethylsilylethyl)pyrazole (615 mg, 3.1 mmol) in dry THF (10 mL) at -78 ° C, under argon was treated with n-BuLi (1.6-M in hexanes, 1.9 mL, 3.1 mmol), stirred for 20 min, treated with ZnCl<sub>2</sub> solution (1-M in Et<sub>2</sub>O, 3.1 mL, 3.1 mmol) and allowed to warm gradually to room temperature. The mixture was treated with 4-chloro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (430 mg, 1.55 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (170 mg, 10 mol%), refluxed for 1 h, diluted with saturated NH<sub>4</sub>Cl solution, extracted with EtOAc, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The resulting brown oil was purified by chromatography [SiO<sub>2</sub>; heptane-EtOAc (3:1)] to give the coupled product as a cream solid. This material was dissolved in MeOH (10 mL), treated with anhydrous HCl (4-M in dioxan, 5 mL), stirred for 17 h, concentrated *in vacuo*, diluted with Et<sub>2</sub>O and filtered to give the *title compound* (216 mg, 40 %) as a cream solid.

20

#### Method L

##### **5-Amino-1-(2-phenylethyl)-1H-pyrazole-4-carboxylic acid**

A mixture of conc. H<sub>2</sub>SO<sub>4</sub> (15 mL) and water (15 mL) was treated with 5-amino-1-(2-phenylethyl)-1H-pyrazole-4-carbonitrile (5.0 g, 23.6 mmol), heated at 60 °C for 1 h, poured into water, extracted with EtOAc, dried (MgSO<sub>4</sub>), concentrated *in vacuo*, and recrystallised (EtOAc/MeOH) to give the *title compound* (2.53 g, 47 %) as a cream solid.

#### Method M

##### **6-Hydroxy-1-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol**

A mixture of 5-amino-1-(2-phenylethyl)-1H-pyrazole-4-carboxylic acid (1.87 g, 8.1 mmol) and urea (1.46 g, 24 mmol) was heated at 180 °C for 5 h, cooled and the resulting solid suspended in boiling water, filtered and washed with water to give the impure *title compound* (2.18 g, 105 %,) as a cream solid.

30

**Method N****4,6-Dichloro-1-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine**

- A solution of 6-hydroxy-1-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (2.13 g, 8.32 mmol) in PhPOCl<sub>2</sub> (8 mL) was heated to 165 °C for 16 h, cooled, poured onto ice and the solid isolated by filtration. The solid was suspended in DCM, filtered through a silica pad and the filtrate was concentrated *in vacuo* to give the *title compound* (556 mg, 23 %) as a colourless oil.

**10 Method O****4-(2-Furyl)-N-(2-hydroxyethyl)-1-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (Example 3)**

- A solution of 6-chloro-4-(2-furyl)-1-(2-phenylethyl)-1H-pyrazolo[3,4-d]pyrimidine (162 mg, 0.5 mmol) in NMP (1 mL) was treated with ethanolamine (60 µL, 1 mmol), heated at 100 °C for 16 h, cooled and purified by chromatography (EtOAc : Heptane, 2:1). The resulting colourless oil was crystallised (MeOH/water) and filtered to give the *title compound* (100 mg, 57 %) as a white solid.

**Method P**

- 20 6-Amino-N-benzyl-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-carboxamide (Example 6)**

- A solution of 4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (210 mg, 1 mmol) in DMF (2 mL) was treated with benzyl isocyanate (123 µL, 1 mmol) and a catalytic amount of DMAP, stirred at room temperature for 1 h, poured into water, extracted with EtOAc, dried (MgSO<sub>4</sub>), concentrated *in vacuo* and purified by preparative HPLC (MeOH/H<sub>2</sub>O gradient) to give the *title compound* (80 mg, 24 %) as a pale yellow solid.

**Method Q****4-(2-Furyl)-1-(4-indolylmethyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine (Example 65)**

- 30** A solution of *tert*-butyl 4-(6-amino-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-1-ylmethyl)indole-1-carboxylate (92 mg, 0.17 mmol) in MeOH (3 mL) was treated with NaOMe (45 mg, 0.84 mmol), refluxed for 2 h, cooled, diluted with water (15 mL) and filtered to give the *title compound* (45 mg, 82 %) as an off white powder.



**Table 2 – Analytical data**

- 5 HPLC is carried out using the following conditions: Column. Supelcosil ABZ<sup>+</sup> (170 x 4.6 mm), particle size 5  $\mu$ M, mobile phase MeOH : 10 mM aq NH<sub>4</sub>OAc (80:50), flow rate 1.0 mL/min., detection wavelength  $\lambda$  = 230 nm. Retention times are provided in Table 2.

Example	Yield(%)	Physical Data
1	96	Mp 85.1 – 85.6 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 2925, 2854, 1604, 1562, 1465, 1377, 1334, 1148, 1014 and 926; NMR (CDCl <sub>3</sub> ) 8.48 (1H, s), 7.80 (1H, d, <i>J</i> 1.2 Hz), 7.60 (1H, d, <i>J</i> 3.6 Hz), 7.27 – 7.17 (5H, m), 6.69 (1H, dd, <i>J</i> 3.6, 2.0 Hz), 4.69 (2H, m) and 3.26 (2H, t, <i>J</i> 8.0 Hz); Anal. Calcd for C <sub>17</sub> H <sub>13</sub> ClN <sub>4</sub> O: C, 67.89; H, 4.00; N, 17.24. Found: C, 62.70; H, 4.06; N, 16.99.
2	67	Mp 90.9 – 91.1 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 2926, 2855, 1609, 1584, 1549, 1488, 1456, 1401, 1160, and 1010; NMR (CDCl <sub>3</sub> ) 8.21 (1H, s), 7.71 (1H, d, <i>J</i> 1.0 Hz), 7.36 (1H, d, <i>J</i> 3.3 Hz), 7.28 – 7.17 (5H, m), 6.61 (1H, dd, <i>J</i> 3.4, 1.8 Hz), 4.53 (2H, m), 3.28 (6H, s) and 3.23 (2H, t, <i>J</i> 7.8 Hz); Anal. Calcd for C <sub>19</sub> H <sub>19</sub> N <sub>5</sub> O: C, 68.45; H, 5.74; N, 21.00. Found: C, 68.40; H, 5.77; N, 20.90.
3	57	Mp 118.6 – 119.3 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3317, 3099, 1613, 1568, 1543 and 1481; NMR $\delta_{\text{H}}$ (400 MHz, CDCl <sub>3</sub> ) 3.21 (2H, t, <i>J</i> 7.5 Hz), 3.60 - 3.68 (2H, m), 3.83 – 3.89 (2H, m), 4.51 (2H, t, <i>J</i> 7.5 Hz), 5.61 (1H, s), 6.59 – 6.63 (1H, m), 7.15 – 7.28 (5H, m), 7.32 – 7.37 (1H, m), 7.69 – 7.74 (1H, m) and 8.22 (1H, s); Anal. Calcd for C <sub>19</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub> : C, 65.32; H, 5.48; N, 20.03. Found: C, 65.24; H, 5.48; N, 19.91.
4	99	Mp 261.9 – 262.7 °C; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 1.61 (9H, s), 6.79 – 6.82 (1H, m), 7.18 (2H, s), 7.44 (1H, d, <i>J</i> 3.0 Hz), 8.08 (1H, s), 8.42 (1H, s); Anal. Calcd for C <sub>14</sub> H <sub>15</sub> N <sub>5</sub> O <sub>3</sub> · 0.4 H <sub>2</sub> O: C, 54.50; H, 5.16; N, 22.70. Found: C, 54.84; H, 5.18; N, 22.35.

5	70	Mp 237.5 – 238.2 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3498, 3341, 3210, 3134, 2924, 2854, 1663, 1639, 1596, 1561, 1463 and 1377; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 6.70 (2H, s), 6.76 – 6.78 (1H, m), 7.40 (1H, d, <i>J</i> 3.5 Hz), 8.04 (1H, s), 8.21 (1H, s) and 12.99 (1H, s).
6	24	Mp 171.2 – 171.6 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3461, 3307, 3200, 3063, 3029, 1643, 1613, 1576, 1557, 1479 and 1379; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 4.56 (2H, d, <i>J</i> 6.0 Hz), 6.81 – 6.83 (1H, m), 7.23 – 7.30 (1H, m), 7.30 – 7.41 (5H, m), 7.49 (1H, d, <i>J</i> 3.5 Hz), 8.10 (1H, s), 8.47 (1H, s) and 9.30 (1H, t, <i>J</i> 6.2 Hz); Anal. Calcd for C <sub>17</sub> H <sub>14</sub> N <sub>6</sub> O <sub>2</sub> · 0.5 H <sub>2</sub> O: C, 59.47; H, 4.40; N, 24.48. Found: C, 59.75; H, 4.22; N, 24.45.
7		Mp 189.6 – 189.8 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3324, 3195, 2955, 2854, 1655, 1580, 1563, 1514, 1483, 1446 and 1432; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.27 (1H, s), 8.06 (1H, d, <i>J</i> 1.2 Hz), 7.44 (1H, d, <i>J</i> 3.6 Hz), 7.33 – 7.18 (3H, m), 6.91 (2H, br s), 6.79 (1H, dd, <i>J</i> 3.2, 1.6 Hz) and 5.43 (2H, s); Anal Calcd for C <sub>16</sub> H <sub>10</sub> N <sub>5</sub> O · 0.4 H <sub>2</sub> O: C, 64.38; H, 4.66; N, 23.46. Found: C, 64.58; H, 4.51; N, 23.18.
8	37	Mp 187.7 – 187.8 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3363, 3323, 3201, 2924, 2854, 1645, 1610, 1580, 1557, 1514, 1483 and 1445; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.30 (1H, s), 8.06 (1H, d, <i>J</i> 0.8 Hz), 7.45 (1H, d, <i>J</i> 3.2 Hz), 7.38 – 7.13 (3H, m), 6.94 (2H, br s), 6.79 (1H, dd, <i>J</i> 3.2, 1.6 Hz) and 5.44 (2H, s); Anal. Calcd for C <sub>16</sub> H <sub>12</sub> ClN <sub>5</sub> O · 0.1 H <sub>2</sub> O: C, 58.67; H, 3.75; N, 21.38. Found: C, 58.97; H, 3.86; N, 20.95.
9		Mp 240.3 – 240.8 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3325, 3204, 2922, 2854, 1652, 1605, 1580, 1555, 1523, 1467, 1377 and 1344; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.28 (1H, s), 8.16 (2H, d, <i>J</i> 8.8 Hz), 8.01 (1H, s), 7.45 – 7.42 (3H, m), 6.76 (1H, m), 6.70 (2H, br s), and 5.57 (2H, s); Anal. Calcd for C <sub>16</sub> H <sub>12</sub> N <sub>6</sub> O <sub>3</sub> · 0.7 H <sub>2</sub> O: C, 49.87; H, 3.77; N, 21.81. Found: C, 50.09; H, 3.46; N, 21.59.
10		Mp 226.8 – 226.9 °C; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.31 (1H, s), 8.06 (1H, d, <i>J</i> 1.2 Hz), 7.75 (1H, d, <i>J</i> 7.6 Hz), 7.67 (1H, s), 7.57 – 7.45 (3H, m), 6.95 (2H, br s), 6.79 (1H, dd, <i>J</i> 3.6, 1.6 Hz) and 5.50 (2H, s); Anal. Calcd for C <sub>17</sub> H <sub>12</sub> N <sub>6</sub> O · 0.75 H <sub>2</sub> O: C, 61.91; H, 4.13; N, 25.48. Found: C,

		62.14; H, 3.81; N, 25.37.
11		Mp 159.4 – 162.2 °C; NMR $\delta_H$ (400 MHz, DMSO) 8.32 (1H, s), 8.07 (1H, s), 7.49 (1H, d, $J$ 8.0 Hz), 7.46 (1H, d, $J$ 3.4 Hz), 7.34 – 7.24 (2H, m), 6.94 (2H, br s), 6.80 (1H, dd, $J$ 3.6, 1.9 Hz) and 5.50 (2H, s).
12		Mp 191.7 – 191.8 °C; NMR $\delta_H$ (400 MHz, DMSO) 8.28 (1H, s), 8.05 (1H, d, $J$ 0.8 Hz), 7.44 (1H, d, $J$ 3.6 Hz), 7.22 (1H, t, $J$ 8.0 Hz), 6.91 (2H, s), 6.85 – 6.72 (5H, m), 5.93 (2H, s) and 3.70 (3H, s). Anal. Calcd. for $C_{17}H_{15}N_5O_2 \cdot 0.2 H_2O$ : C, 62.84; H, 4.78; N, 21.55. Found: C, 62.91; H, 4.71; N, 21.22.
13		IR $\nu_{max}$ (Nujol)/ $cm^{-1}$ 2923, 2854, 1616, 1588, 1552, 1531, 1487, 1456, 1377, 1245 and 1042; NMR $\delta_H$ (400 MHz, DMSO) 8.30 (1H, s), 8.07 (1H, s), 7.45 (1H, d, $J$ 3.6 Hz), 7.20 – 7.11 (3H, m), 6.92 – 6.71 (10H, m), 5.38 (2H, s), 4.98 – 4.89 (4H, m) and 3.66 (9H, s); Anal. Calcd for $C_{33}H_{21}N_5O_4 \cdot H_2O$ : C, 68.38; H, 5.74; N, 12.08; Found: C, 68.74; H, 5.47; N, 12.10; $M/Z$ 562 ( $M+H$ ) <sup>+</sup> .
14	28	Mp 210.3 – 210.4 °C; IR $\nu_{max}$ (Nujol)/ $cm^{-1}$ 3339, 3203, 3061, 1655, 1582, 1561, 1407, 1454, 1228 and 758; NMR $\delta_H$ (400 MHz, DMSO) 5.47 (2H, s), 6.77 – 6.80 (1H, m), 6.93 (2H, s), 7.04 – 7.09 (1H, m), 7.10 – 7.16 (1H, m), 7.19 – 7.26 (1H, m), 7.31 – 7.38 (1H, m), 7.44 (1H, d, $J$ 3.0 Hz), 8.06 (1H, s) and 8.28 (1H, s).
15		Mp 226.9 – 227.7 °C; IR $\nu_{max}$ (Nujol)/ $cm^{-1}$ 3331, 3111, 2925, 2854, 1638, 1574, 1488, 1460, 1378, 1032 and 887; NMR $\delta_H$ (400 MHz, DMSO) 8.40 (1H, s), 8.17 (1H, s), 7.75 (1H, s), 7.21 (1H, t, $J$ 7.2 Hz), 7.10 – 7.00 (3H, m), 6.88 (1H, dd, $J$ 3.6, 1.6 Hz) and 5.39 (2H, s); Anal. Calcd for $C_{17}H_{15}H_5O \cdot HCl \cdot H_2O$ : C, 56.75; H, 5.04; N, 19.46. Found: C, 57.03; H, 5.06; N, 19.10.
16	40	Mp 202.3 – 202.4 °C; IR $\nu_{max}$ (Nujol)/ $cm^{-1}$ 3408, 3327, 3212, 2924, 2854, 1724, 1640, 1607, 1579, 1558, 1510, 1485 and 1448; NMR $\delta_H$ (400 MHz, DMSO) 8.30 (1H, s), 8.06 (1H, d, $J$ 1.2 Hz), 7.87 (1H, m), 7.81 (1H, s), 7.52 – 7.45 (3H, m), 6.94 (2H, s), 6.79 (1H, dd, $J$ 3.6, 2.0

		Hz), 5.51 (2H, s) and 3.83 (3H, s).
17		Mp 239.2 – 239.4 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3318, 3136, 2922, 2854, 1656, 1634, 1614, 1586, 1463, 1377, 1300 and 1148; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.37 (1H, s), 8.11 (1H, s), 7.88 (2H, d, <i>J</i> 8.4 Hz), 7.58 (1H, d, <i>J</i> 3.4 Hz), 7.42 (2H, d, <i>J</i> 8.3 Hz), 6.83 (1H, dd, <i>J</i> 3.6, 1.7 Hz), 5.6 (2H, s) and 3.18 (3H, s); Anal. Calcd for C <sub>17</sub> H <sub>15</sub> N <sub>5</sub> O <sub>3</sub> S · HCl · 0.5 H <sub>2</sub> O: C, 49.22; H, 4.13; N, 16.88. Found: C, 49.05; H, 3.93; N, 16.53.
18		NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.37 (1H, s), 8.16 (1H, s), 7.73 (1H, s), 7.27 – 7.16 (5H, m), 6.87 (1H, dd, <i>J</i> 3.4, 1.6 Hz), 4.44 (2H, d, <i>J</i> 7.1 Hz) and 3.16 (2H, t, <i>J</i> 7.2 Hz); Anal. Calcd for C <sub>17</sub> H <sub>15</sub> N <sub>5</sub> O · HCl: C, 59.74; H, 4.72; N, 20.48. Found: C, 59.46; H, 4.76; N, 20.11.
19		NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.32 (1H, s), 8.12 (1H, d, <i>J</i> 1.2 Hz), 6.84 (1H, dd, <i>J</i> 3.6, 2.0 Hz), 4.04 (2H, d, <i>J</i> 7.6 Hz), 1.92 (1H, m), 1.65 – 1.50 (5H, m) and 1.16 – 1.14 (5H, m); Retention time 5.59 min.
20	99	Mp 306.0 – 306.3 °C; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.32 (1H, s), 8.08 (1H, s), 7.85 (1H, m), 7.77 (1H, s), 7.48 (3H, m), 6.81 (1H, dd, <i>J</i> 3.6, 1.6 Hz), 7.0 (2H, br s) and 5.50 (2H, s); Retention time 0.62 min.
21		Mp 191.4 – 191.5 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3456, 3328, 3121, 2924, 2854, 1662, 1633, 1573, 1484, 1454, 1375 and 1032; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.33 (1H, s), 8.14 (1H, s) 7.66 (1H, br s), 6.86 (1H, br s), 4.89 (1H, br m) and 1.45 (6H, br m); Anal. Calcd for C <sub>12</sub> H <sub>13</sub> N <sub>5</sub> O · HCl · 1.25 H <sub>2</sub> O: C, 47.69; H, 5.50; N, 23.17. Found: C, 47.90; H, 5.21; N, 23.00.
22		Mp 219.0 – 219.4 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 2924, 2854, 1644, 1574, 1461, 1377, 1328 and 1112; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.35 (1H, s), 8.10 (1H, s), 7.69 (2H, d, <i>J</i> 8.0 Hz), 7.55 (1H, s), 7.39 (2H, d, <i>J</i> 8.0 Hz), 6.82 (1H, t, <i>J</i> 1.6 Hz) and 5.54 (2H, s); Anal. Calcd for C <sub>17</sub> H <sub>12</sub> F <sub>3</sub> N <sub>5</sub> O · HCl · 0.5 H <sub>2</sub> O: C, 50.44; H, 3.49; N, 17.30. Found: C, 50.73; H, 3.23; N, 17.19.

23		Mp 218 °C; NMR $\delta_H$ (400 MHz, DMSO) 8.36 (1H, s), 8.16 (1H, s), 7.73 (1H, s), 6.87 (1H, t, $J$ 1.8 Hz), 4.19 (2H, m), 7.80 (2H, m), 1.32 – 1.23 (4H, m) and 0.84 (3H, t, $J$ 6.8 Hz); Anal. Calcd for $C_{14}H_{17}N_5O \cdot HCl$ : C, 54.63; H, 5.89; N, 22.74. Found: C, 54.55; H, 6.04; N, 22.44.
24		Mp 235.5 – 236.2 °C; NMR $\delta_H$ (400 MHz, DMSO) 8.20(1H, s), 8.12 (1H, s), 7.61 (1H, d, $J$ 3.2 Hz), 7.50 – 7.43 (1H, m), 7.14 – 7.11 (2H, m), 6.83 (1H, dd, $J$ 3.6, 1.6 Hz) and 5.44 (2H, s); Anal. Calcd for $C_{16}H_{11}F_2N_5O \cdot HCl \cdot 0.75 H_2O$ : C, 50.94; H, 3.61; N, 18.56. Found: C, 50.96; H, 3.32; N, 18.20.
25	10	NMR $\delta_H$ (400 MHz, DMSO) 5.61 (2H, s), 6.79 – 6.83 (1H, m), 7.52 (1H, d, $J$ 3.5 Hz), 7.82 (1H, dd, $J$ 8.0, 5.5 Hz), 8.09 (1H, s), 8.12 (1H, s), 8.76 (1H, s); $M/Z$ 293 ( $M+H$ ) <sup>+</sup> .
26	41	Mp 177.0 – 177.1 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3456, 3331, 3211, 3142, 3121, 2726, 1731, 1651, 1587, 1559, 1488, 1462, 1377, 1235 and 755; NMR $\delta_H$ (400 MHz, DMSO) 1.20 (3H, t, $J$ 7.0 Hz), 4.15 (2H, q, $J$ 7.0 Hz) 5.06 (2H, s), 6.78 – 6.81 (1H, m), 6.94 (2H, s), 7.44 (1H, d, $J$ 3.5 Hz), 8.06 (1H, s) and 8.28 (1H, s); Anal. Calcd for $C_{13}H_{13}N_5O_3$ : C, 54.35; H, 4.56, N, 24.37. Found: C, 54.22; H, 4.58; N, 24.01.
27	95	Mp 291.9 – 192.0 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3371, 3329, 3204, 3141, 2726, 1704, 1658, 1579, 1456, 1378, 956 and 789; NMR $\delta_H$ (400 MHz, DMSO) 4.96 (2H, s), 6.78 – 6.80 (1H, m), 6.92 (2H, s), 7.44 (1H, d, $J$ 3.5 Hz), 8.05 – 8.07 (1H, m), 8.26 (1H, s) and 13.09 (1H, s); Anal. Calcd for $C_{11}H_9N_5O_3 \cdot 0.3 H_2O$ : C, 49.93; H, 3.66, N, 26.46. Found: C, 50.22; H, 3.46; N, 26.12.
28	20	Mp 204.5 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3485, 3322, 2925, 1651, 1587, 1378, 1232 and 709; NMR $\delta_H$ (400 MHz, DMSO) 5.14 (2H, br s), 5.57 (2H, s), 7.01 – 7.14 (3H, m), 7.20 – 7.31 (2H, m), 7.59 (1H, dd, $J$ 5.0, 1.0 Hz), 7.98 (1H, d, $J$ 3.5 Hz) and 8.19 (1H, s); Retention time 4.87 min
29	59	Mp 249.8 – 249.9 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3441, 3292, 3058, 2645, 1705, 1668, 1630, 1582, 1561, 1457, 1381 and 1215; NMR $\delta_H$ (400 MHz, DMSO) 5.25 (2H, s), 6.16 – 6.78 (2H, s), 6.91 – 6.96 (1H, m), 7.23 (1H, t, $J$ 7.0 Hz), 7.88 – 7.99 (3H, m), 8.24 (1H, s), 8.37 (1H, d, $J$ 5.0

		Hz), 8.49 (1H, s) and 11.41 (1H, s); Anal. Calcd for $C_{16}H_{13}N_7O_3 \cdot HCl \cdot 3 H_2O$ : C, 43.49; H, 4.56; N, 22.19. Found: C, 43.60; H, 4.01; N, 21.95.
30	47	IR $\nu_{max}$ (Nujol)/ $cm^{-1}$ 3604, 3342, 3152, 3090, 2601, 1659, 1629, 1574, 1558, 1526 and 1460; NMR $\delta_H$ (400 MHz, DMSO) 4.66 – 5.19 (2H, s), 5.59 (2H, s), 6.82 – 6.85 (1H, m), 7.60 (1H, d, $J$ 3.5 Hz), 7.62 – 7.67 (2H, m), 8.07 – 8.09 (1H, m), 8.11 (1H, d, $J$ 1.0 Hz), 8.14 – 8.17 (1H, m), 8.39 (1H, s); Anal. Calcd for $C_{16}H_{12}N_6O_3 \cdot HCl \cdot 0.75 H_2O$ : C, 49.75; H, 3.78, N, 21.76. Found: C, 49.92; H, 3.39; N, 21.33.
31		Mp 190.9 – 191.7 °C; IR $\nu_{max}$ (Nujol)/ $cm^{-1}$ 3407, 3171, 3089, 2923, 2854, 1651, 1633, 1578, 1485, 1455 and 1377; NMR $\delta_H$ (400 MHz, DMSO) 8.40 (1H, s), 8.17 (1H, s), 7.76 (1H, s), 7.30 – 7.15 (5H, m), 6.88 (1H, dd, $J$ 3.5, 1.6 Hz), 4.23 (2H, t, $J$ 7.0 Hz), 2.60 (2H, t, $J$ 7.3 Hz) and 2.17 – 2.10 (2H, m); Retention time 5.42 min.
32	94	NMR $\delta_H$ (400 MHz, DMSO) 4.70 – 5.44 (2H, s), 5.49 (2H, s), 6.86 (1H, s), 7.12 (1H, s), 7.27 (2H, t, $J$ 7.5 Hz), 7.45 (1H, t, $J$ 7.5 Hz), 7.66 (1H, d, $J$ 2.5 Hz), 8.39 (1H, s) and 9.48 – 10.63 (2H, s); M/Z 307 (M+H) <sup>+</sup> .
33	19	IR $\nu_{max}$ (Nujol)/ $cm^{-1}$ 3328, 3193, 2925, 2854, 1650, 1598, 1561, 1513, 1456, 1430 and 1377; NMR $\delta_H$ (400 MHz, DMSO) 8.84 (1H, d, $J$ 4.4 Hz), 8.54 (1H, s), 8.43 (1H, d $J$ 8.0 Hz), 8.04 (1H, m), 7.60 (1H, dd, $J$ 6.8, 5.2 Hz), 7.34 (1H, m), 7.22 (1H, m), 7.13 (1H, m) 7.07 (1H, m), 7.03 (2H, s) and 5.50 (2H, s).
34	58	Mp 276.8 – 277.2 °C; NMR $\delta_H$ (400 MHz, DMSO) 4.29 (2H, d, $J$ 6.0 Hz), 4.89 (2H, s), 6.77 – 6.81 (1H, m), 6.88 (2H, s), 7.21 – 7.37 (5H, m), 7.44 (1H, d, $J$ 3.5 Hz), 8.04 – 8.07 (1H, m), 8.26 (1H, s) and 8.50 (1H, t, $J$ 6.0 Hz).
35	58	Mp 276.8 – 277.2 °C; NMR $\delta_H$ (400 MHz, DMSO) 4.29 (2H, d, $J$ 6.0 Hz), 4.89 (2H, s), 6.77 – 6.81 (1H, m), 6.88 (2H, s), 7.21 – 7.37 (5H, m), 7.44 (1H, d, $J$ 3.5 Hz), 8.04 – 8.07 (1H, m), 8.26 (1H, s) and 8.50 (1H, t, $J$ 6.0 Hz).

36	29	Mp 279.9 – 281.0 °C; NMR $\delta_H$ (400 MHz, DMSO) 5.08 (2H, s), 6.78 – 6.82 (1H, m), 6.90 (2H, s), 7.13 (1H, d), <i>J</i> 8.0 Hz), 7.36 (1H, t, <i>J</i> 8.0 Hz), 7.42 – 7.49 (2H, m), 7.74 – 7.79 (1H, m), 8.05 – 8.09 (1H, m), 8.28 (1H, s) and 10.52 (1H, s).
37	49	Mp 247.9 – 249.4 °C; NMR $\delta_H$ (400 MHz, DMSO) 4.28 (2H, d, <i>J</i> 6.0 Hz), 4.86 (2H, s), 6.26 (1H, d, <i>J</i> 2.5 Hz), 6.38 – 6.41 (1H, m), 6.77 – 6.80 (1H, m), 6.88 (2H, s), 7.44 (1H, d, <i>J</i> 3.5 Hz), 7.57 – 7.60 (1H, m), 8.04 – 8.07 (1H, m), 8.25 (1H, s) and 8.52 (1H, t, <i>J</i> 5.5 Hz).
38	31	Mp 200.0 – 200.1 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3473, 3181, 3078, 2923, 1646, 1572, 1461, 1376, 792 and 768; NMR $\delta_H$ (400 MHz, DMSO) 5.19 (2H, br s), 5.59 (2H, s), 6.98 – 7.12 (3H, m), 7.20 – 7.29 (1H, m), 7.58 (1H, d, <i>J</i> 3.5 Hz) and 8.59 (1H, s); Retention time 4.64 min.
39		Mp 223.2 – 225.1 °C; NMR $\delta_H$ (400 MHz, DMSO) 8.29 (1H, s), 8.09 (1H, d, <i>J</i> 1.2 Hz), 7.58 (1H, m), 7.53 (1H, d, <i>J</i> 3.2 Hz), 6.81 (1H, dd, <i>J</i> 3.6, 2.0 Hz), 6.41 (1H, dd, <i>J</i> 3.2, 2.0 Hz), 6.36 (1H, d, <i>J</i> 2.8 Hz) and 5.40 (2H, s).
40	61	IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3495, 3321, 3210, 3118, 2727, 1635, 1604, 1579, 1478, 1464, 1390 and 1175; NMR $\delta_H$ (400 MHz, DMSO) 2.36 (3H, s), 6.78 – 6.79 (1H, m), 7.43 – 7.45 (4H, m), 7.92 (2H, d, <i>J</i> 8.5 Hz), 8.05 (1H, s) and 8.52 (1H, s).
41		Mp 218.7 – 219.5 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3495, 3321, 2925, 2854, 1615, 1596, 1570, 1512, 1481, 1452, and 1377; NMR $\delta_H$ (400 MHz, DMSO) 8.34 (1H, s), 7.46 (1H, s), 7.34 (1H, s), 7.21 (2H, m), 7.13 (1H, m), 7.05 (1H, m), 6.97 (2H, br s), 5.47 (2H, s) and 4.20 (3H, s).
42	11	Mp 250.5 – 251.2 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3483, 3354, 2924, 2854, 1616, 1601, 1575, 1503, 1454, 1418 and 1377; NMR $\delta_H$ (400 MHz, DMSO) 13.08 (1H, br s), 8.37 (1H, s), 7.38 – 7.06 (6H, m) 6.72 (2H, br s) and 5.48 (2H, s).
43	59	Mp 267.4 – 271.5 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3461, 3290, 3194, 1664, 1589, 1465, 1377, 1291, 1235, 1157, 1014 and 795; NMR $\delta_H$ (400 MHz, DMSO) 3.71 (3H, s), 5.06 (2H, s), 6.65 (1H, dd, <i>J</i> 8.0, 2.0 Hz), 6.78 – 6.81 (1H, m), 6.89 (2H, s), 7.09 (1H, d, <i>J</i> 9.0 Hz), 7.21 (1H, d, <i>J</i> 3.0 Hz),

		7.26 – 7.30 (1H, m), 7.45 (1H, d, <i>J</i> 3.0 Hz), 8.05 – 8.08 (1H, m), 8.28 (1H, s) and 10.31 (1H, s).
44	71	Mp 231.1 – 231.2 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3462, 3298, 3213, 3111, 1651, 1586, 1558, 1487, 1456, 1377, 1280, 1169, 1009 and 765; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 2.72 (2H, t, <i>J</i> 7.0 Hz), 3.24 – 3.35 (2H, m), 4.80 (2H, s), 6.77 – 6.82 (1H, m), 6.88 (2H, s), 7.16 – 7.23 (3H, m), 7.24 – 7.33 (2H, m), 7.44 (1H, d, <i>J</i> 3.0 Hz), 8.02 – 8.09 (2H, m) and 8.25 (1H, s).
45	15	Mp 276.2 – 278.5 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3448, 3288, 3199, 1669, 1588, 1557, 1456, 1378, 1309, 1106, 888 and 757; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 5.15 (2H, s), 6.76 – 6.83 (1H, m), 6.90 (2H, s), 7.11 – 7.20 (2H, m), 7.23 – 7.32 (1H, m), 7.42 – 7.48 (1H, m), 7.83 – 7.93 (1H, m), 8.04 – 8.09 (1H, m), 8.28 (1H, s) and 10.12 (1H, s).
46	22	NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.39 (1H, m), 8.29 (1H, s), 8.06 (1H, d, <i>J</i> 1.2 Hz), 7.72 – 7.68 (2H, m), 7.45 – 7.31 (2H, m), 6.92 (2H, s), 6.79 (1H, dd, <i>J</i> 3.2, 1.6 Hz), 5.47 (2H, s) and 2.74 (3H, d, <i>J</i> 4.8 Hz); Anal. Calcd for C <sub>18</sub> H <sub>16</sub> N <sub>6</sub> O <sub>2</sub> · 0.5 H <sub>2</sub> O: C, 60.50; H, 4.79; N, 23.52. Found: C, 60.32; H, 4.63; N, 23.50.
47	33	NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.29 (1H, s), 8.06 (1H, s), 7.44 (1H, d, <i>J</i> 3.4 Hz), 7.40 – 7.20 (4H, m), 6.92 (2H, s), 6.79 (1H, dd, <i>J</i> 3.5, 1.9 Hz) 5.46 (2H, s), 2.94 (3H, br s) and 2.85 (3H, br s).
48	75	NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 3.79 (3H, s), 4.25 (2H, d, <i>J</i> 6.0 Hz), 4.90 (2H, s), 6.75 – 6.81 (1H, m), 6.84 – 7.01 (4H, m), 7.18 – 7.28 (2H, m), 7.44 (1H, d, <i>J</i> 3.5 Hz), 8.06 (1H, s), 8.27 (1H, s), 8.29 (1H, t, <i>J</i> 6.0 Hz). Anal. Calcd. for C <sub>19</sub> H <sub>18</sub> N <sub>6</sub> O <sub>3</sub> · 0.5 H <sub>2</sub> O: C, 58.91; H, 4.94; N, 21.69. Found: C, 60.20; H, 5.34; N, 21.33; M/Z 379 (M+H) <sup>+</sup> .
49	75	NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 4.33 (2H, d, <i>J</i> 5.0 Hz), 4.90 (2H, s), 6.79 (1H, s), 6.89 (2H, s), 7.11 – 7.23 (2H, m), 7.26 – 7.40 (2H, m), 7.44 (1H, d, <i>J</i> 3.0 Hz), 8.06 (1H, s), 8.27 (1H, s) and 8.52 (1H, t, <i>J</i> 5.5 Hz); M/Z 367 (M+H) <sup>+</sup> .



50	89	Mp. 265.8 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3360, 3290, 3147, 2924, 2854, 1637, 1608, 1575, 1497, 1465 and 1377; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 13.8 (1H, br s), 8.45 (1H, s), 8.02 (1H, s), 7.22 (1H, br s), 7.13 (4H, s), 5.39 (2H, s) and 2.26 (3H, s).
51	18	Mp. 287.9 °C; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.77 (1H, br s), 8.40 (1H, s), 7.37 – 7.11 (4H, m) and 5.50 (2H, s).
52	80	NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.35 (1H, s), 8.14 (1H, dd, <i>J</i> 8.1, 1.1 Hz), 8.07 (1H, d, <i>J</i> 1.2 Hz), 7.67 – 7.56 (2H, m), 7.47 (1H, d, <i>J</i> 3.5 Hz), 6.95 (2H, s), 6.81 – 6.79 (2H, m) and (5.80 (2H, s); Anal. Calcd for C <sub>16</sub> H <sub>12</sub> N <sub>6</sub> O <sub>3</sub> · 0.3 H <sub>2</sub> O: C, 56.24; H, 3.72; N, 24.59. Found: C, 56.41; H, 3.48; N, 24.15.
53		IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 2924, 2854, 1605, 1581, 1465, 1377, 1156 and 1018; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 12.0 (1H, br s), 10.39 (1H, br s), 8.52 (1H, s), 8.16 (1H, s), 7.81 (2H, br s), 7.75 (1H, d, <i>J</i> 4.0 Hz), 7.60 (1H, s), 7.38 (1H, d, <i>J</i> 2.4 Hz), 7.23 (1H, t, <i>J</i> 7.6 Hz), 7.05 – 6.85 (5H, m) and 5.49 (2H, s); Anal. Calcd for C <sub>20</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub> S <sub>2</sub> · 0.4 H <sub>2</sub> O: C, 47.57; H, 3.13; N, 13.87. Found: C, 47.70; H, 3.20; N, 13.53.
54	22	NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 5.36 (2H, s), 6.78 – 6.82 (1H, m), 6.87 (1H, s), 6.89 – 6.95 (2H, m), 6.98 – 7.04 (3H, m), 7.21 (1H, t, <i>J</i> 8.0 Hz), 7.38 – 7.40 (1H, m), 7.46 (1H, d, <i>J</i> 3.5 Hz), 7.81 (1H, dd, <i>J</i> 5.0, 1.0 Hz), 8.07 (1H, s), 8.28 (1H, s) and 10.39 (1H, s); M/Z 453 (M+H) <sup>+</sup> .
55	40	Mp 245.3 - 246.1 °C; IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3666, 2922, 1638, 1460, 1378, 1229 and 757; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 5.49 (2H, s), 7.12 - 7.28 (3H, m), 7.31 - 7.42 (2H, m), 8.06 (1H, d, <i>J</i> 2.0 Hz) and 8.53 (1H, s); Retention time 2.10 min.
56		IR $\nu_{\max}$ (Nujol)/cm <sup>-1</sup> 3600 – 2500 br, 2921, 2853, 1659, 1633, 1574, 1556, 1462, 1378 and 1031; NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.38 (1H, s), 8.13 (1H, d, <i>J</i> 1.2 Hz), 7.37 – 7.29 (2H, m), 7.12 (1H, m), 6.88 – 6.84 (2H, m) and 5.54 (2H, s).

57	6	NMR $\delta_H$ (400 MHz, DMSO) 3.68 (3H, s), 5.49 (2H, s), 6.60 (1H, d, $J$ 7.5 Hz), 6.79 – 6.82 (1H, m), 6.91 (2H, s), 7.02 – 7.09 (1H, m), 7.18 (2H, d, $J$ 4.5 Hz), 7.47 (1H, d, $J$ 3.5 Hz), 7.23 (1H, s), 7.84 (1H, s), 8.07 (1H, s), 8.31 (1H, s) and 10.13 (1H, s); $M/Z$ 451 ( $M+H$ ) <sup>+</sup> .
58	14	NMR $\delta_H$ (400 MHz, DMSO) 8.73 (1H, br s), 8.40 (1H, s), 8.15 (1H, m), 8.08 (1H, s), 7.64 (1H, d, $J$ 5.1 Hz) and 5.61 (2H, s).
59	5	Mp 278.5 – 279.0 °C; NMR $\delta_H$ (400 MHz, DMSO) 8.44 (1H, s), 8.15 (1H, m), 8.08 (1H, s), 7.97 (1H, d, $J$ 2.3 Hz), 7.10 (1H, s), 7.10 (2H, br s) and 6.00 (2H, s).
60	22	Mp 193.3 – 193.4 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3289, 2934, 1661, 1642, 1582, 1514, 1460 and 1377; NMR $\delta_H$ (400 MHz, DMSO) 8.76 (1H, s), 8.40 (1H, s), 7.44 (1H, t, $J$ 7.6 Hz), 7.25 (2H, m) 7.07 (1H, s) and 5.50 (2H, s).
61	25	Mp 193.3 – 193.4 °C; NMR $\delta_H$ (400 MHz, DMSO) 5.61 (2H, s), 7.17 (2H, br s), 7.61 - 7.67 (2H, m), 8.07 - 8.11 (2H, m), 8.12 - 8.19 (1H, m), 8.23 (1H, d, $J$ 3.0 Hz) and 8.43 (1H, s); Retention time 4.70 min.
62	93	Mp 177.8 - 178.3 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3302, 2925, 1634, 1462, 1377, 774 and 778; NMR $\delta_H$ (400 MHz, DMSO) 5.50 (2H, s), 7.08 (1H, s), 7.23 - 7.31 (2H, m), 7.45 (1H, t, $J$ 7.5 Hz), 8.09 (1H, d, $J$ 3.0 Hz), 8.22 (1H, d, $J$ 3.0 Hz) and 8.41 (1H, s); Retention time 1.75 min.
63	67	IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3162, 2920, 1551, 1574, 1464, 1378, 1072 and 766; NMR $\delta_H$ (400 MHz, DMSO) 8.51 (1H, s), 8.04 (1H, d, $J$ 2.5 Hz), 7.44 (1H, t, $J$ 8.0 Hz), 7.31 (1H, br s), 7.27 - 7.20 (2H, m), 7.10 (1H, s) and 5.49 (2H, s).
64	81	mp 171 - 172 °C; IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3252, 2922, 1667, 1619, 1466, 1378, 1261, 1169, 769 and 751; NMR $\delta_H$ (400 MHz, DMSO) 8.59 (1H, s), 8.10 (1H, d, $J$ 2.5 Hz), 7.51 (1H, br s), 7.25 (1H, t, $J$ 8.0 Hz), 6.90 - 6.82 (2H, m), 6.82 - 6.77 (1H, d, $J$ 8.0 Hz), 5.43 (2H, s) and 3.72 (3H, s).
65	82	IR $\nu_{max}$ (Nujol)/cm <sup>-1</sup> 3318, 2923, 1640, 1455, 1455, 1378 and 750; NMR $\delta_H$ (400 MHz, DMSO) 11.13 (1H, br s), 8.23 (1H, s), 8.05 (1H, d, $J$ 1.0 Hz), 7.43 (1H, d, $J$ 3.5 Hz), 7.34 - 7.28 (2H, m), 7.00 (1H, t, $J$ 7.0 Hz),

		6.89 (2H, br s), 6.78 (1H, dd, <i>J</i> 3.5, 2.0 Hz), 6.73 (1H, d, <i>J</i> 6.5 Hz), 6.53 - 6.49 (1H, m) and 5.63 (2H, s).
66		NMR $\delta_{\text{H}}$ (400 MHz, DMSO) 8.25 (1H, s), 8.06 - 8.04 (1H, m), 7.99 (1H, d, <i>J</i> 8.5 Hz), 7.68 (1H, d, <i>J</i> 3.5 Hz), 7.43 (1H, d, <i>J</i> 3.5 Hz), 7.26 (1H, t, <i>J</i> 7.5 Hz), 6.99 (1H, d, <i>J</i> 6.5 Hz), 6.93 (2H, br s), 6.86 (1H, d, <i>J</i> 4.0 Hz), 6.79 - 6.77 (1H, m), 5.65 (2H, s) and 1.61 (9H, s).

### Adenosine Receptor Binding

#### 5 Binding Affinities at hA<sub>2A</sub> Receptors

The compounds were examined in an assay measuring *in vitro* binding to human adenosine A<sub>2A</sub> receptors by determining the displacement of the adenosine A<sub>2A</sub> receptor selective radioligand [<sup>3</sup>H]-CGS 21680 using standard techniques. The results are summarised in Table 3.

10

**Table 3**

Example	K <sub>i</sub> (nM)
Example 11	9
Example 12	2
Example 14	2
Example 15	2
Example 22	6
Example 24	2
Example 28	5
Example 30	4
Example 31	2
Example 32	4
Example 33	12
Example 51	71

Example 55	16
Example 56	8

### Evaluation of potential anti-Parkinsonian activity *in vivo*

#### **Haloperidol-induced hypolocomotion model**

- 5 It has previously been demonstrated that adenosine antagonists, such as theophylline, can reverse the behavioural depressant effects of dopamine antagonists, such as haloperidol, in rodents (Mandhane S.N. *et al.*, Adenosine A<sub>2</sub> receptors modulate haloperidol-induced catalepsy in rats. *Eur. J. Pharmacol.* 1997, **328**, 135 - 141). This approach is also considered a valid method for screening drugs with potential antiparkinsonian effects.
- 10 Thus, the ability of novel adenosine antagonists to block haloperidol-induced deficits in locomotor activity in mice can be used to assess both *in vivo* and potential antiparkinsonian efficacy.

#### Method

- 15 Female TO mice (25-30g) obtained from TUCK, UK, are used for all experiments. Animals are housed in groups of 8 [cage size – 40 (width) x 40 (length) x 20 (height)cm] under 12hr light/dark cycle (lights on 08:00hr), in a temperature (20 ± 2°C) and humidity (55 ± 15%) controlled environment. Animals have free access to food and water, and are allowed at least 7 days to acclimatize after delivery before experimental use.

20

#### Drugs

- Liquid injectable haloperidol (1 ml Serenace ampoules from Baker Norton, Harlow, Essex, each containing haloperidol BP 5 mg, batch # P424) are diluted to a final concentration of 0.02 mg/ml using saline. Test compounds are typically prepared as
- 25 aqueous suspensions in 8% Tween. All compounds are administered intraperitoneally in a volume of 10 ml/kg.

#### Procedure

- 1.5 hours before testing, mice are administered 0.2 mg/kg haloperidol, a dose that reduces
- 30 baseline locomotor activity by at least 50%. Test substances are typically administered 5-60 minutes prior to testing. The animals are then placed individually into clean, clear polycarbonate cages [20 (width) x 40 (length) x 20 (height) cm, with a flat perforated,

Perspex lid]. Horizontal locomotor activity is determined by placing the cages within a frame containing a 3 x 6 array of photocells linked to a computer, which tabulates beam breaks. Mice are left undisturbed to explore for 1 hour, and the number of beams breaks made during this period serves as a record of locomotor activity which is compared with  
5 data for control animals for statistically significant differences.

### 6-OHDA Model

Parkinson's disease is a progressive neurodegenerative disorder characterised by symptoms of muscle rigidity, tremor, paucity of movement (hypokinesia), and postural instability. It  
10 has been established for some time that the primary deficit in PD is a loss of dopaminergic neurones in the substantia nigra which project to the striatum, and indeed a substantial proportion of striatal dopamine is lost (ca 80-85%) before symptoms are observed. The loss of striatal dopamine results in abnormal activity of the basal ganglia, a series of nuclei which regulate smooth and well co-ordinated movement (Blandini F. *et al.*, Glutamate and  
15 Parkinson's Disease. *Mol. Neurobiol.* 1996, 12, 73 - 94). The neurochemical deficits seen in Parkinson's disease can be reproduced by local injection of the dopaminergic neurotoxin 6-hydroxydopamine into brain regions containing either the cell bodies or axonal fibres of the nigrostriatal neurones.

20 By unilaterally lesioning the nigrostriatal pathway on only one-side of the brain, a behavioural asymmetry in movement inhibition is observed. Although unilaterally-lesioned animals are still mobile and capable of self maintenance, the remaining dopamine-sensitive neurones on the lesioned side become supersensitive to stimulation. This is demonstrated by the observation that following systemic administration of dopamine agonists, such as  
25 apomorphine, animals show a pronounced rotation in a direction contralateral to the side of lesioning. The ability of compounds to induce contralateral rotations in 6-OHDA lesioned rats has proven to be a sensitive model to predict drug efficacy in the treatment of Parkinson's Disease.

### 30 Animals

Male Sprague-Dawley rats, obtained from Charles River, are used for all experiments. Animals are housed in groups of 5 under 12hr light/dark cycle (lights on 08:00hr), in a temperature ( $20 \pm 2^{\circ}\text{C}$ ) and humidity ( $55 \pm 15\%$ ) controlled environment. Animals have

free access to food and water, and are allowed at least 7 days to acclimatize after delivery before experimental use.

#### Drugs

- 5 Ascorbic acid, desipramine, 6-OHDA and apomorphine (Sigma-Aldrich, Poole, UK). 6-OHDA is freshly prepared as a solution in 0.2% ascorbate at a concentration of 4 mg/mL prior to surgery. Desipramine is dissolved in warm saline, and administered in a volume of 1 mL/kg. Apomorphine is dissolved in 0.02% ascorbate and administered in a volume of 2 mL/kg. Test compounds are suspended in 8% Tween and injected in a volume of 2 mL/kg.

10

#### Surgery

- 15 minutes prior to surgery, animals are given an intraperitoneal injection of the noradrenergic uptake inhibitor desipramine (25 mg/kg) to prevent damage to non-dopamine neurones. Animals are then placed in an anaesthetic chamber and anaesthetised using a mixture of oxygen and isoflurane. Once unconscious, the animals are transferred to a stereotaxic frame, where anaesthesia is maintained through a mask. The top of the animal's head is shaved and sterilised using an iodine solution. Once dry, a 2 cm long incision is made along the midline of the scalp and the skin retracted and clipped back to expose the skull. A small hole is then drilled through the skull above the injection site. In order to lesion the nigrostriatal pathway, the injection cannula is slowly lowered to position above the right medial forebrain bundle at -3.2 mm anterior posterior, -1.5 mm medial lateral from bregma, and to a depth of 7.2 mm below the duramater. 2 minutes after lowering the cannula, 2  $\mu$ L of 6-OHDA is infused at a rate of 0.5  $\mu$ L/min over 4 minutes, yielding a final dose of 8  $\mu$ g. The cannula is then left in place for a further 5 minutes to facilitate diffusion before being slowly withdrawn. The skin is then sutured shut using Ethicon W501 Mersilk, and the animal removed from the stereotaxic frame and returned to its homecage. The rats are allowed 2 weeks to recover from surgery before behavioural testing.

#### Apparatus

- 30 Rotational behaviour is measured using an eight station rotameter system provided by Med Associates, San Diego, USA. Each station is comprised of a stainless steel bowl (45 cm diameter x 15 cm high) enclosed in a transparent Plexiglas cover running around the edge of the bowl, and extending to a height of 29 cm. To assess rotation, rats are placed in cloth jacket attached to a spring tether connected to optical rotameter positioned above the bowl,

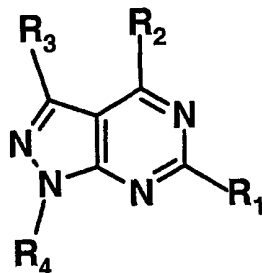
which assesses movement to the left or right either as partial (45°) or full (360°) rotations. All eight stations are interfaced to a computer that tabulated data.

Procedure

- 5 To reduce stress during drug testing, rats are initially habituated to the apparatus for 15 minutes on four consecutive days. On the test day, rats are given an intraperitoneal injection of test compound 30 minutes prior to testing. Immediately prior to testing, animals are given a subcutaneous injection of a subthreshold dose of apomorphine, then placed in the harness and the number of rotations recorded for one hour. The total number of full
- 10 contralateral rotations during the hour test period serves as an index of antiparkinsonian drug efficacy.

CLAIMS

1. Use of a compound of formula (I):



(I)

5

wherein

R<sub>1</sub> is selected from alkyl, alkoxy, aryloxy, alkylthio, arylthio, aryl, halogen, CN, NR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>COR<sub>6</sub>, NR<sub>5</sub>CONR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>CO<sub>2</sub>R<sub>8</sub> and NR<sub>5</sub>SO<sub>2</sub>R<sub>8</sub>;

R<sub>2</sub> is selected from heteroaryl attached via an unsaturated carbon;

- 10 R<sub>3</sub> is selected from H, alkyl, halogen, OR<sub>5</sub>, SR<sub>5</sub> and NR<sub>6</sub>R<sub>7</sub>;

R<sub>4</sub> is selected from H, acyclic alkyl, CONR<sub>6</sub>R<sub>7</sub>, CONR<sub>5</sub>NR<sub>6</sub>R<sub>7</sub>, COR<sub>6</sub>, CO<sub>2</sub>R<sub>8</sub> and SO<sub>2</sub>R<sub>8</sub>;

R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are independently selected from H, alkyl and aryl, or where R<sub>6</sub> and R<sub>7</sub> are in an NR<sub>6</sub>R<sub>7</sub> group, R<sub>6</sub> and R<sub>7</sub> may be linked to form a heterocyclic group, or where R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are in a (CONR<sub>5</sub>NR<sub>6</sub>R<sub>7</sub>) group, R<sub>5</sub> and R<sub>6</sub> may be linked to form a heterocyclic group;

15 and

R<sub>8</sub> is selected from alkyl and aryl,

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for the treatment or prevention of a disorder in which the blocking of purine receptors may be beneficial.

20

2. Use according to claim 1 wherein R<sub>1</sub> is selected from alkyl, alkoxy, thioalkyl, NR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>COR<sub>6</sub>, NR<sub>5</sub>CONR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>CO<sub>2</sub>R<sub>8</sub> and NR<sub>5</sub>SO<sub>2</sub>R<sub>8</sub>.

3. Use according to claim 1 wherein R<sub>1</sub> is selected from NR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>COR<sub>6</sub>,  
25 NR<sub>5</sub>CONR<sub>6</sub>R<sub>7</sub>, NR<sub>5</sub>CO<sub>2</sub>R<sub>8</sub> and NR<sub>5</sub>SO<sub>2</sub>R<sub>8</sub>.

4. Use according to claim 1 wherein R<sub>1</sub> is selected from NR<sub>6</sub>R<sub>7</sub>.



5. Use according to claim 1 wherein  $R_1$  is selected from  $NH_2$ .
6. Use according to claim 1 wherein  $R_1$  is selected from  $NR_5CONR_6R_7$ ,  $NR_5COR_6$ ,  
5  $NR_5CO_2R_8$  and  $NR_5SO_2R_8$ , and  $R_5$  is H or alkyl.
7. Use according to claim 1 wherein  $R_1$  is selected from  $NR_5CONR_6R_7$ ,  $NR_5COR_6$ ,  
 $NR_5CO_2R_8$  and  $NR_5SO_2R_8$ , and  $R_5$  is H.
- 10 8. Use according to claim 1 wherein  $R_1$  is selected from haloalkyl and arylalkyl.
9. Use according to any preceding claim wherein  $R_2$  is a 5- or 6- membered monocyclic heteroaryl group.
- 15 10. Use according to any preceding claim wherein  $R_2$  is a heteroaryl group which is attached to the pyrimidine ring of formula (I) such that a heteroatom is adjacent to said unsaturated carbon atom attached to the pyrimidine ring.
11. Use according to any preceding claim wherein  $R_2$  is an N, O or S-containing heteroaryl  
20 group.
12. Use according to any of claims 1 to 11 wherein  $R_2$  is unsubstituted in at least one ortho position.
- 25 13. Use according to any of claims 1 to 11 wherein  $R_2$  is unsubstituted at both ortho positions.
14. Use according to any preceding claim wherein  $R_2$  is selected from furyl, thienyl, pyridyl, pyrazolyl and thiazolyl.
- 30 15. Use according to any preceding claim wherein  $R_2$  is selected from 2-furyl, 2-thienyl, 2-thiazolyl, 3-pyrazolyl and 2-pyridyl.

16. Use according to any preceding claim wherein  $R_2$  is 2-furyl.
17. Use according to any preceding claim wherein  $R_3$  is hydrogen.
- 5 18. Use according to any of claims 1 to 17 wherein  $R_4$  is selected from H and substituted acyclic alkyl.
19. Use according to claim 18 wherein  $R_4$  is acyclic alkyl substituted by substituted or unsubstituted aryl, cycloalkyl, non-aromatic heterocyclyl,  $CO_2R_5$ ,  $CONR_6R_7$ ,  $CONR_5NR_6R_7$
- 10 and  $C(=NR_5)NR_6R_7$ .
20. Use according to claim 19 wherein  $R_4$  is acyclic alkyl substituted by substituted or unsubstituted aryl or  $CONR_6R_7$ .
- 15 21. Use according to claim 20 wherein  $R_4$  is methyl substituted by substituted or unsubstituted aryl or  $CONR_6R_7$ .
22. Use according to any of claims 1 to 17 wherein  $R_4$  is selected from  $(CR_9R_{10})_nR_{11}$  wherein n is 1 to 6,  $R_9$  and  $R_{10}$  are independently selected from H, alkyl and aryl, and  $R_{11}$  is
- 20 selected from substituted and unsubstituted aryl, cycloalkyl, non-aromatic heterocyclic,  $CO_2R_5$ ,  $CONR_6R_7$ ,  $CONR_5NR_6R_7$  and  $C(=NR_5)NR_6R_7$ .
23. Use according to claim 22 wherein n is 1.
- 25 24. Use according to claim 22 or 23 wherein  $R_9$  and  $R_{10}$  are independently selected from H and alkyl, preferably H.
25. Use according to claim 22, 23 or 24 wherein  $R_{11}$  is selected from substituted or unsubstituted aryl and  $CONR_6R_7$ .
- 30 26. Use according to any of claims 22 to 25 wherein  $R_{11}$  is a substituted aryl group represented by the formula  $Ar(R_{12})_a(R_{13})_b(R_{14})_c$  wherein Ar is an aryl group; wherein  $R_{12}$ ,  $R_{13}$  and  $R_{14}$  are substituent group(s), the same or different; and wherein a, b and c are 0 or 1 such that  $a+b+c \geq 1$ .

27. Use according to claim 26 wherein  $R_{12}$ ,  $R_{13}$  and  $R_{14}$  are independently selected from  $NR_6R_7$ , alkyl, alkoxy, halogen,  $NO_2$ , CN, hydroxy,  $NHOH$ , CHO,  $CONR_6R_7$ ,  $CO_2R_5$ ,  $NR_5COR_6$ ,  $NR_5CO_2R_8$ ,  $NR_5SO_2R_8$ ,  $OCO_2R_8$  and aryl.
- 5
28. Use according to claim 26 wherein  $R_{12}$ ,  $R_{13}$  and  $R_{14}$  are independently selected from  $NR_6R_7$ , alkyl and halogen.
29. Use according to claim 27 or 28 wherein  $R_{12}$ ,  $R_{13}$  and  $R_{14}$  are independently selected
- 10 from alkyl, and said alkyl is substituted alkyl and is selected from alkoxyalkyl, hydroxyalkyl, aminoalkyl and haloalkyl.
30. Use according to claim 27 or 28 wherein  $R_{12}$ ,  $R_{13}$  and  $R_{14}$  are independently selected from unsubstituted alkyl,  $NH_2$  and fluoro.
- 15
31. Use according to any of claims 19 to 30 wherein said substituted or unsubstituted aryl group is substituted or unsubstituted phenyl, thienyl, furyl, pyridyl or indolyl.
32. Use according to claim 31 wherein said substituted or unsubstituted aryl group is substituted and unsubstituted phenyl, thienyl, furyl or pyridyl.
- 20
33. Use according to claim 22, 23 or 24 wherein  $R_{11}$  is selected from  $CONR_6R_7$ ,  $R_6$  is H and  $R_7$  is selected from H, unsubstituted alkyl, arylalkyl and aryl.
34. Use according to any one of claims 1 to 17 wherein  $R_4$  is selected from  $CONR_6R_7$ ,  $R_6$
- 25 is H and  $R_7$  is selected from arylalkyl.
35. Use according to claim 34 wherein  $R_7$  is selected from arylmethyl.
36. Use according to any preceding claim wherein  $R_5$  to  $R_8$  are independently selected
- 30 from lower alkyl.
37. Use according to claim 1 wherein  $R_1$  is  $NH_2$ ,  $R_2$  is 2-furyl,  $R_3$  is H and  $R_4$  is arylmethyl.

38. Use according to claim 1 wherein the compound of formula (I) is selected from Examples 1 to 66 disclosed herein.

- 5 39. Use according to claim 1 wherein the compound of formula (I) is selected from:
- 4-(2-furyl)-1-(3-methoxybenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine;
  - 1-(2-fluorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine;
  - 4-(2-furyl)-1-(3-methylbenzyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine;
  - 1-(2,6-difluorobenzyl)-4-(2-furyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine;
  - 10 4-(2-furyl)-1-(3-phenylpropyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine; and
  - 1-(2-fluorobenzyl)-4-(2-pyridyl)-1H-pyrazolo[3,4-d]pyrimidine-6-amine.

40. A method of treating or preventing a disorder in which the blocking of purine receptors may be beneficial comprising administration to a subject in need of such  
15 treatment an effective dose of a compound as set out in any one of claims 1 to 39 or a pharmaceutically acceptable salt thereof.

41. A use or method according to any one of claims 1 to 40 wherein the disorder is caused by the hyperfunctioning of purine receptors.

20

42. A use or method according to any one of claims 1 to 41 wherein the purine receptors are adenosine receptors.

43. A use or method according to claim 42 wherein the adenosine receptors are A<sub>2A</sub>  
25 receptors.

44. Use or method according to any preceding claim wherein the disorder is a movement disorder.

30 45. A use or method according to claim 44 wherein the movement disorder is Parkinson's disease.

46. A use or method according to claim 45 for treatment of drug-induced Parkinsonism, post-encephalitic Parkinsonism, Parkinsonism induced by poisoning or post-traumatic Parkinson's disease.

5 47. A use or method according to claim 44 wherein the movement disorder is progressive supernuclear palsy, Huntingtons disease, multiple system atrophy, corticobasal degeneration, Wilsons disease, Hallerorden-Spatz disease, progressive pallidal atrophy, Dopa-responsive dystonia-Parkinsonism, spasticity or other disorders of the basal ganglia which result in dyskinesias.

10

48. A use or method according to any one of claims 44 to 47 wherein the compound of formula (I) is in combination with one or more additional drugs useful in the treatment of movement disorders, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

15

49. A use or method according to claim 48 wherein said additional drug(s) useful in the treatment of movement disorders is/are a drug useful in the treatment of Parkinson's disease.

20 50. A use or method according to claim 48 or 49 wherein the or one of the additional drugs is L-DOPA or a dopamine agonist.

51. A use or method according to any one of claims 1 to 43 wherein said disorder is depression, cognitive or memory impairment, acute or chronic pain, ADHD or narcolepsy.

25

52. A use or method according to claim 51 wherein said cognitive or memory impairment disorder is Alzheimer's Disease.

53. Use of a compound as set out in any one of claims 1 to 39 or a pharmaceutically  
30 acceptable salt thereof in the manufacture of a medicament for neuroprotection in a subject.

54. A method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of a compound as set out in any one of claims 1 to 39 or a pharmaceutically acceptable salt thereof.
- 5 55. A use or method according to claim 53 or 54 wherein said medicament or said method is for neuroprotection in a subject suffering from or at risk from a neurodegenerative disorder.
56. A use or method according to claim 55 wherein said neurodegenerative disorder is a  
10 movement disorder.
57. A use or method according to claim 56 wherein said movement disorder is a disorder as set out in claim 45, 46 or 47.
- 15 58. A use or method according to any one of claims 1 to 57 wherein the subject is human.
59. A compound according to any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, for use in therapy.
- 20 60. A compound according to any one of claims 1 to 39, or a pharmaceutically acceptable salt or prodrug thereof, *per se*, other than compounds wherein R<sub>2</sub> is selected from pyrazolopyrimidines.
- 25 61. A compound according to claim 60 wherein the compound is selected from those wherein R<sub>2</sub> is a 5- or 6- membered monocyclic heteroaryl group.

## INTERNATIONAL SEARCH REPORT

PCT/GB 02/00075

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/505 C07D487/04 A61P25/28 //(C07D487/04, 239:00, 231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 21617 A (BARALDI PIER GIOVANNI ;MEDCO RES INC (US)) 6 May 1999 (1999-05-06) claim 1	1-61
A	EP 0 390 112 A (MERRELL DOW PHARMA) 3 October 1990 (1990-10-03) claim 1	1-61
	-/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

25 April 2002

Date of mailing of the international search report

07/05/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Steendijk, M

## INTERNATIONAL SEARCH REPORT

T/GB 02/00075

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEBIB M ET AL: "1-Phenylpyrazolo[3,4-d]pyrimidines as Adenosine antagonists: the Effects of Substituents at C4 and C6" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 5, no. 2, 1997, pages 311-322, XP002086425 ISSN: 0968-0896 table 2	1-61
A	COCUZZA A J ET AL: "Use of the suzuki reaction for the synthesis of aryl-substituted heterocycles as corticotropin-releasing hormone (CRH) antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 7, 5 April 1999 (1999-04-05), pages 1063-1066, XP004162586 ISSN: 0960-894X page 1064	1-61
A	WO 94 13643 A (PFIZER ; FARACI WILLIAM STEPHEN (US); WELCH WILLARD MCKOWAN JR (US)) 23 June 1994 (1994-06-23) claim 1	1-61



## INTERNATIONAL SEARCH REPORT

PCT/GB 02/00075

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9921617	A	06-05-1999	US 5939432 A	17-08-1999
			US 6323214 B1	27-11-2001
			AU 9671798 A	17-05-1999
			CA 2302396 A1	06-05-1999
			EP 1025106 A2	09-08-2000
			WO 9921617 A2	06-05-1999
			US 6177444 B1	23-01-2001
			US 6194449 B1	27-02-2001
			US 2001047008 A1	29-11-2001
EP 0390112	A	03-10-1990	AT 162791 T	15-02-1998
			AU 630439 B2	29-10-1992
			AU 5221590 A	04-10-1990
			CA 2013380 A1	29-09-1990
			CN 1045973 A ,B	10-10-1990
			DE 69031989 D1	05-03-1998
			DE 69031989 T2	03-09-1998
			DK 390112 T3	23-09-1998
			EP 0390112 A2	03-10-1990
			ES 2114524 T3	01-06-1998
			FI 95910 B	29-12-1995
			GR 3026173 T3	29-05-1998
			HU 53648 A2	28-11-1990
			IL 93892 A	28-11-1994
			JP 2289570 A	29-11-1990
			JP 2954971 B2	27-09-1999
			KR 168647 B1	15-01-1999
			NO 173996 C	02-03-1994
			NZ 233078 A	25-11-1993
			PT 93588 A ,B	20-11-1990
			US 5391739 A	21-02-1995
			US 5329007 A	12-07-1994
			US 5256650 A	26-10-1993
			ZA 9002280 A	28-12-1990
WO 9413643	A	23-06-1994	AT 175961 T	15-02-1999
			AU 690527 B2	30-04-1998
			AU 5454894 A	04-07-1994
			AU 713804 B2	09-12-1999
			AU 7843198 A	01-10-1998
			BR 9307659 A	29-06-1999
			CA 2150483 A1	23-06-1994
			CN 1092768 A ,B	28-09-1994
			CZ 9501585 A3	17-01-1996
			DE 69323212 D1	04-03-1999
			DE 69323212 T2	27-05-1999
			DK 674624 T3	13-09-1999
			EG 20397 A	28-02-1999
			EP 0674624 A1	04-10-1995
			ES 2126661 T3	01-04-1999
			FI 935674 A	18-06-1994
			GR 3029568 T3	30-06-1999
			HU 67457 A2	28-04-1995
			IL 107946 A	24-09-1998
			JP 2862374 B2	03-03-1999
			JP 7509725 T	26-10-1995
			KR 170567 B1	18-02-1999
			MX 9308042 A1	31-08-1994

# INTERNATIONAL SEARCH REPORT

T/GB 02/00075

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9413643	A	NO 952395 A	16-08-1995
		NO 985494 A	16-08-1995
		NZ 257770 A	24-02-1997
		PL 309356 A1	02-10-1995
		RU 2142946 C1	20-12-1999
		WO 9413643 A1	23-06-1994
		US 2002016333 A1	07-02-2002
		US 5712303 A	27-01-1998
		US 6103900 A	15-08-2000
		ZA 9309404 A	15-06-1995